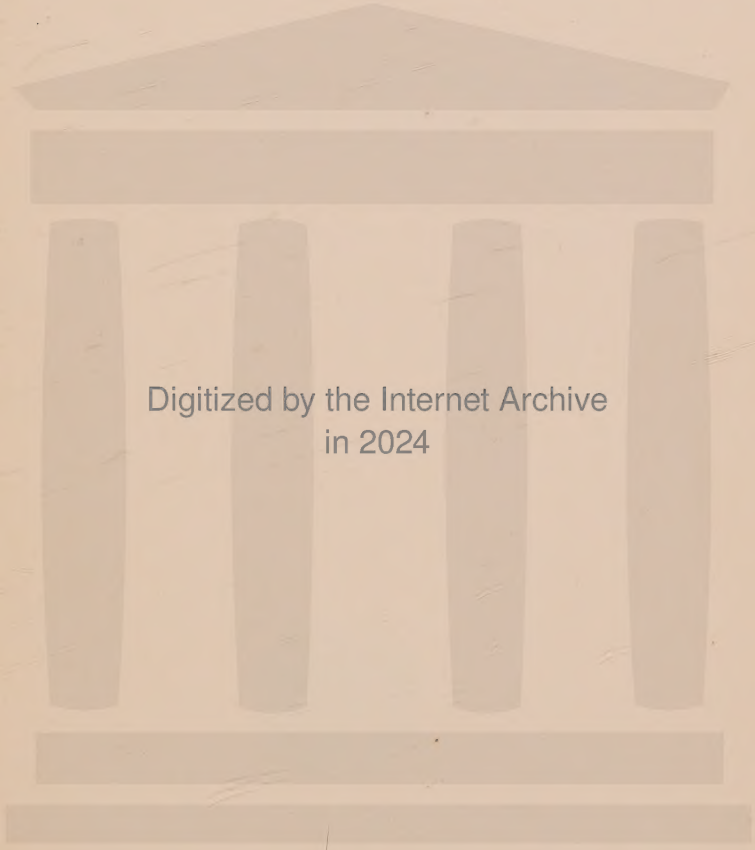

ALLERGIC DISEASES

DIAGNOSIS AND TREATMENT OF BRONCHIAL ASTHMA, HAY-FEVER AND OTHER ALLERGIC DISEASES

BY

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TO MY FRIEND

DR. C. LANDSTEINER

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PREFACE

During a visit to the United States in 1919 I had the pleasure of meeting Dr. Chandler Walker in Boston and saw his work on human sensitization. Upon returning to Holland I began to investigate this matter myself. After a short time we were able to confirm the principles laid down by Walker. However we found that cases of sensitizations to the "allergens" used by Walker were much less frequent here than they apparently were in Walker's cases. Consequently we could apply specific treatment in only a few cases, which induced us to search for other methods. In this way we found the tuberculin-treatment of allergic diseases, which we later completed with milk and sulphur treatment as additional measures.

By this method we were able to cure 50% of our asthma cases; 30% were improved but not cured, 20% remained uninfluenced. Our results with hayfever and migraine were much better than those with asthma.

The fact that 50% of our cases of asthma were either uninfluenced or only partly cured, stimulated us to further research. As a result of investigations in Holland and Switzerland we came to the conclusion that in other low regions as well, the main causes for the occurrence of asthmatic and other allergic attacks are dependent upon influences of climate. We furthermore found that these factors of climate are in general to be identified with a particular sort of allergens (climate-allergens or miasms) occurring in the air in the lower countries and lacking—or present in a minor degree—in high altitudes. These allergens were shown to be, for the most part, decomposition of various material, or products of metabolism of various animal or vegetable parasites, the occurrence of which

in certain regions is due to the influence of climate, humidity of air, temperature, etc.

These considerations modified our opinions on the etiology and treatment of allergic diseases to a considerable degree. Indeed we had deviated so far from the original conceptions of Dr. Walker and other American workers in this field that we thought the time had come to publish our viewpoints in book form in the English language.

The study of allergic diseases along modern lines was started only a few years ago. Much work on these subjects is going on in different clinics and laboratories and at this moment it is still impossible to give positive and definite answers to a number of questions regarding these matters. In this small volume, therefore, the author has not attempted to give final conclusions. He fully realizes that on many points the chapter has not yet been closed.

As a matter of fact, on one particular subject we had to change our opinion between sending the MS to press and reading the final proof sheets. This was due to the fact that during that period our experiments with pure air treatment (miasmproof rooms) had succeeded so well that we were tempted to write an additional chapter on this point. As it was, we could only briefly mention this method in the body of the book.

Our first publication on a miasmfree room was made in April, 1924. (Proc. Royal Soc. of Medic., Vol. XVII.) The principles laid down in that publication have been worked out so completely that we have opened a clinic for allergic diseases in Leiden, based entirely on the principle of pure air treatment in miasmproof chambers. Moreover, we have already induced a number of patients to have a small miasmfree chamber built in their own bedrooms, in order that pure air treatment can be applied at home.

The results of this treatment have by far exceeded our expectations. If the reader finds that only a small space in

the book is dedicated to this matter, we beg him to realize that the importance of the new method is not in direct proportion to the number of pages covered, but far surpasses it.

The author is anxious to state that his own work mentioned in the book has been done in collaboration with his assistants, Dr. Bien, Nijk, Varekamp, Kremer, Einthoven, Jr. and Miss Germ, all of whom deserve his heartiest thanks.

THE AUTHOR

DIAGNOSIS AND TREATMENT OF BRONCHIAL ASTHMA, HAY-FEVER AND OTHER ALLERGIC DISEASES

DIAGNOSIS

The term " allergic disease " has been introduced into medical literature by American investigators (Cooke and others) to designate a number of conditions which show one common etiological characteristic, viz., hypersensitiveness to proteins or other substances which are innocuous to normal people. For the most part these patients suffer from acute attacks, while in the interval between two attacks they are in good health. Often, however, especially in the more severe cases, they present symptoms of their illness continuously, but suffer from acute exacerbations.

To these allergic diseases belong hay-fever, most cases of bronchial asthma, many forms of urticaria, eczema and other skin diseases, Quincke's œdema, and some cases of migraine and epilepsy.

The name " allergic disease " is not entirely fitting since the term " allergy " was introduced by von Pirquet to designate a state of heightened sensitiveness to tuberculin induced by some change (tuberculous infection) occurring in the body during post-uterine life, whereas the allergic condition in hay-fever, bronchial asthma, etc., is often inherited. The writer, however, is of the opinion that the introduction of a new name, even if more correct, would only bring about still further confusion; hence he prefers to keep to the term " allergic disease."

As the characteristic feature of all allergic diseases is

hypersensitiveness to drugs or protein material, it is advisable to begin a discussion of these diseases with a general study of the phenomenon of hypersensitiveness.

The following points will have to be investigated:

1. Hypersensitiveness to drugs.
2. Hypersensitiveness to various pollens.
3. Hypersensitiveness to so-called animal proteins.
4. Hypersensitiveness to foodstuffs.
5. Hypersensitiveness to bacterial products.
6. Hypersensitiveness to colloidal substances of unknown composition, whose presence in the air is due to climatic influences (miasms).

1. HYPERSENSITIVENESS TO DRUGS

Every physician knows that the intensity of the action of most drugs—even if given in exactly the same quantity—is not the same for every patient. The sensitiveness of the patient varies from case to case. Before entering into a discussion of this point, it is well to draw a sharp line between two different forms of hypersensitiveness.

There are many instances in which a drug exerts an action much more intense than would be expected on the basis of the experience with this drug in other cases, but in which the nature of the symptoms produced will be similar to those observed in normal individuals. These, then, may be called cases of purely *quantitative* hypersensitiveness. One person may be much more sensitive to the action of alcohol or nicotine than another person, but both will, after application of a large enough dose of the drug, respond with the same symptoms, drunkenness after taking alcohol, dizziness, headache, vomiting, after taking nicotine. Similar quantitative differences in action are shown by many drugs. Lipoid-soluble narcotics are not very apt

to show such differences, although even here they may be found.[1, 2] Alkaloids and coal-tar products present the phenomenon much more often. One of the best studied examples is the case of cocaine. Doses of fifty milligrammes may be injected even intravenously into men without any danger, and instances are known where subcutaneous injection of a solution containing more than one gramme of cocaine was tolerated without any untoward symptoms, but on the other hand cases have been recorded in which sixteen, forty, or sixty milligrammes of cocaine caused death in apparently normal persons (cases collected by Hatcher and Eggleston).[3] Similar differences in action have been recorded for novocaine and other drugs. But in all these cases the point of interest is, that the subject dying from a dose which is below the quantity tolerated easily by other people dies with exactly the same symptoms as every other man would show if large enough quantities of the same drug had been administered to him.

The cause of these differences in sensitiveness is not exactly known, but some work to elucidate this point has been done. I refer to the study of Reid Hunt[4] and his co-workers on the resistance of mice to acetonitrile and to investigations on the influence of nutritive factors on the sensitiveness of animals to drugs, made by Mansfeld,[5] Ellinger,[6] Salant[7] and his co-workers, and Hooper, Kolls and Wright,[8] etc. Recently the author[9] has pointed out a number of factors which influence the sensitivity of animals to drugs.

Entirely different from these instances of quantitative hypersensitiveness is a number of cases in which introduction of a small amount of a drug into a human being gives rise to the onset of a series of symptoms which have no relation at all to the "normal" action of the drug. The

symptoms mentioned may be slight and consist of urticaria, eczemata or other skin affections, rhinorrhœa, or conjunctivitis, or the symptoms may be more serious and may be accompanied by a "shoc hémoclasique" and present bronchial asthma and diarrhœa; sometimes collapse and even death may ensue. These symptoms may be induced in apparently normal persons by the ingestion of small quantities of drugs which are wholly innocuous for other people, they may appear the very first time that the patient takes a certain drug, or may suddenly present themselves in a person who has taken the same drug for many years without any untoward results. Symptoms of hypersensitiveness may be shown—as has been pointed out above—by people who never suffered from similar affections; often, however, these persons are already suffering from some allergic disease. We saw ten cases of hypersensitiveness to aspirin among two hundred asthma patients and in all these people the dominant symptom of the hypersensitive reaction was a violent attack of asthma. Often a sufferer of drug idiosyncrasy, although not suffering from an allergic disease himself, will belong to a family in which allergic diseases or idiosyncrasies occur.

The most important drugs which occasionally induce idiosyncratic symptoms are antipyrine, salicylic acid, quinine, veronal, luminal, salvarsan, derivatives of paraphenylenediamine, boric acid, iodine, bromides, mercury salts, arsenic, strychnine, etc. The nature of the symptoms of hypersensitiveness sometimes seems to be dependent on the drug; antipyrine, for example, tends to induce a rather serious form of eczema which especially involves the genital region. Often also the nature of the symptoms seems to be due to an inherent factor in the patient. A sufferer from asthma will usually show asthmatic

attacks as the phenomenon of drug idiosyncrasy (*v.* cases of hypersensitiveness to aspirin in asthmatics cited above), while epileptics will tend to show epileptic phenomena as idiosyncratic symptoms, etc.

In these last cases one obtains the impression that the drug does not so much act as a nocuous factor *per se,* but that it simply augments an allergic reaction already going on—or latent—in the human body. Recently we published some arguments which seem to make this conception more probable. As a matter of fact we could show that *in vitro,* acting on isolated organs, those drugs which may induce symptoms of hypersensitiveness in man may, in minute quantities, augment the action of other drugs,[10, 11] and also that the blood of sufferers from allergic diseases is less able to combine with alkaloids or with drugs like salicylic acid [12] than is the blood of normal men. In the body of hypersensitive people, then, drugs will often be in a "free" state so that they may be able to exert their augmenting influence on other—in this case, allergic—reactions happening in the body. Extensive references to the literature on the subject of hypersensitiveness to drugs are given by Doerr,[13] Coca,[14] and Bayer.[15]

2. HYPERSENSITIVENESS TO VARIOUS POLLENS

In 1873, Blackley showed that attacks of hay-fever are caused by the presence in the air of certain species of pollen which, on coming in contact with the nasal membranes or conjunctivæ of certain people, give rise to attacks of rhinitis and conjunctivitis, sneezing, etc. Blackley furthermore found that not only the mucous membranes of sufferers from hay-fever but also their skin are hypersensitive to pollen. This discovery, made by Blackley, and amplified by Dunbar and others, has in

later years become of great importance, since it has formed a basis for all the later work on diseases due to hypersensitiveness.

A definite explanation of the origin of hypersensitiveness to pollen cannot yet be given. Weichardt and Wolff-Eisner were the first to call attention to the similarity between hay-fever and anaphylactic shock. This point will be discussed later on, but some facts relative to it may be mentioned here. If a relation exists between anaphylaxis and hay-fever it would be surmised that a sufferer from hay-fever must have been "sensitized" by a first contamination with pollen, and after some time shows shock symptoms on coming into renewed contact with the same pollen. As has been emphasized by Coca, Cooke and van der Veer and others, there are some facts which do not harmonize with this conception. First, pollen is not a good antigen. If injected into animals it does not, or only very incompletely, sensitize the animal. It might be supposed that hay-fever patients are extraordinarily apt to be sensitized, so that an experiment which fails in animals might succeed in these persons. This, however, is not the case, as it has been shown that people hypersensitive to a certain pollen cannot be artificially sensitized to other pollens by injecting extracts of these pollens intracutaneously. Moreover, in hay-fever hereditary factors demonstrating themselves as increased disposition to allergic diseases generally play an important part. Of 504 allergics studied by Cooke and van der Veer, 48.4 per cent. had familial allergic antecedents. Of 300 cases studied in the author's institute about fifty per cent. showed hereditary factors.

Hay-fever patients are often sensitive to one pollen only, but in many cases they are sensitive to more than

one pollen or to pollen and other proteins. This matter has been carefully studied by Cooke and van der Veer. As shown in the table, taken from one of their papers,[16] they found among 530 cases of hay-fever 57.7 per cent. sensitive to one pollen only. In all other cases multiple sensitization was present.

A.	Early hay-fever	96 cases	= 18%	
	Late hay-fever	276 cases	= 52%	
	Early and late hay-fever	158 cases	= 30%	
B.	With 1 sensitization	318 cases	= 57.7%	
	With 2 sensitizations	172 cases	= 31.2%	
	With 3 sensitizations	42 cases	= 7.6%	= 42.3%
	Over 3 sensitizations	19 cases	= 3.5%	

Another point of interest is that instances seem to exist in which a person showed symptoms of hay-fever the very first time he came into contact with a certain pollen. Similar facts are also seen in drug hypersensitiveness and in hypersensitiveness to foodstuffs. Coca considers this point brings strong evidence against the anaphylactic theory of hay-fever. The whole question of the relationship between anaphylaxis and allergic diseases has been extensively treated by Coca [17] and later by Doerr. The last-named author has recently given an excellent survey of the entire literature relating to this matter. We will refer to this question later in this book.

3. HYPERSENSITIVENESS TO SO-CALLED ANIMAL PROTEINS

Experienced clinicians of former times already knew that some asthma patients always show attacks of their disease if they come in contact with horses, but probably de Besche was the first to appreciate the real importance of this fact and to bring it to general notice. In his first

paper de Besche, who himself suffered from "horse" asthma, described his personal experiences.[18] He had noticed that asthmatic attacks always set in if he entered a horse stable. Subcutaneous injection of a few c. c. of horse serum induced violent attacks of asthma in him, followed by a period of lessened sensitiveness to the emanations of horses. Later he reported fourteen similar cases of horse asthma.[19] A number of analogous cases have been published by others. Only in recent years, however, has the importance of these facts in relation to the etiology of bronchial asthma and other allergic diseases been appreciated. This is mainly due to the work of Chandler Walker,[20] Coca,[17] and Cooke [21] in America, of Widal and his school in France,[22] and of Frugoni [23] in Italy.

It is generally admitted now, that in a certain number of cases asthmatic attacks are caused by the inhalation of horse protein (horse dandruff), or of the hair of the dog, cat, or rabbit, or of feathers (in pillows), etc. In French literature is described the case of a dealer in sheep, who, after having followed his trade for some twenty years without in any way being disturbed, became sensitized to the exhalations of sheep and suffered from asthmatic attacks whenever he came into their vicinity.

There is no doubt, then, that cases of sensitization to animal proteins really exist; it is, however, useful to call attention to the fact that these cases are rare. Perhaps some hundreds of cases of animal sensitization have been described, but tens of thousands of asthmatics exist whose attacks have no relation at all to animal proteins. This will be discussed more extensively in a subsequent section of this book. According to the author's view, the real importance of the work of the above-mentioned authors, who were the pioneer workers in "protein sensitization,"

lies in the circumstance that they brought to light the fact that almost all cases of asthma are due to some kind of hypersensitiveness. In this way our knowledge of this disease has been extended to a considerable degree.

As in the case of hay-fever, an attempt has also been made, in these cases of sensitization to animal proteins, to find a relation to anaphylaxis, and the difficulties which arise against this conception are almost the same as those met with in the former case. Animal proteins, like those of horse dandruff and dog's hair, are not very good anaphylactogens. Friedberger,[24] who recently reviewed the literature on this question, reported that experiments in which an attempt was made to induce anaphylactic symptoms by the injection or inhalation of horse dandruff in guinea-pigs sensitized by injections of extracts of horse dandruff gave only very meagre results. Also the hypersensitiveness to animal protein is often an inherited property. Furthermore, attempts have often been made, but in vain, to demonstrate the presence of antibodies to animal protein in the blood of patients showing sensitization to these proteins; and injection of the blood of such patients into guinea-pigs has often failed to induce a state of passive anaphylaxis in these animals. There seems, then, to be a large amount of evidence which cannot be brought into agreement with a theory that considers horse asthma and similar forms of this disease to be anaphylactic phenomena. Later it will be shown that the greater part of these difficulties can be removed.

It must be mentioned that allergic symptoms may be caused not only by the inhalation of animal proteins but also by bringing the proteins into contact with the patient's skin. In this relation a case described by Markley [25] may be cited. A woman suffered from a skin affection on the

neck and shoulders which resisted all treatment. It was, however, found that she kept a guinea-pig in a cage and, when she cleaned the cage, the animal was allowed to walk round her bare neck. The places on her skin which in this way had been in frequent contact with products of the guinea-pig's skin and hair had become hypersensitive to these products. The skin of other parts of her body was not sensitive to guinea-pig's hair. After withdrawal of the animal, her skin affection disappeared.

4. HYPERSENSITIVENESS TO FOODSTUFFS

Hypersensitiveness to foodstuffs was undoubtedly the earliest recognized form of allergy. Nearly everybody knows that the ingestion of strawberries, lobster, crab, shrimps, and various fishes, and also meat and eggs, may cause disagreeable and even serious symptoms in some people, whereas other people are able to eat any amount of these foodstuffs without experiencing any such effects. With reference to the prohibition in the Hebrew creed against eating pork, it is interesting to note that this meat seems more apt to induce allergic symptoms than any other meat which is generally eaten. The allergic symptoms arising in certain individuals after eating the foodstuffs mentioned may consist of gastro-intestinal disturbances (vomiting, diarrhœa) or of skin eruptions (for the most part urticaria), or they may be of the asthmatic or hay-fever type (bronchial asthma, rhinorrhœa, conjunctivitis, sneezing).

Besides the foodstuffs mentioned a great number of others may induce allergic symptoms—the milk of various animals; beans; fruits like apples, peaches, prunes; various cereals such as wheat, oats, etc. Sometimes hypersensitiveness is strictly specific. Cases are known in which

only the eggs of ducks and no other eggs nor any other foodstuff caused allergic symptoms; some babies are hypersensitive to cow's milk only, etc. But on the other hand many instances are known of multiple sensitization to foodstuffs. According to our experience these last-mentioned cases are more frequent than those of sensitization to one substance only. We have studied a case of a very decided hypersensitiveness to eggs in a child of three years. Ingestion of twenty milligrammes of egg-yolk caused vomiting and asthmatic attacks, but this child was also hypersensitive—though in a lesser degree—to egg-white, to milk, and to some other foodstuffs. Recently we described a case of hypersensitiveness to at least ten foodstuffs (strawberries, other berries, red, black, and white currants, spinach, some other vegetables, grapes and champagne, but not to red Bordeaux and Rhine wine) in a woman of forty years.[26] We have noticed that in asthmatics intolerance to milk, butter and cheese is a common finding, while sometimes eggs are also badly tolerated by them. Apart from this we found that a certain number of asthmatics (about four per cent. of all cases seen) seems to be more or less intolerant to nearly every foodstuff. These people are only free from all asthmatic signs if they have been fasting for two days. As soon as they start eating, asthmatic signs will reappear after about eight hours, and although some foods are much more nocuous to them than others, nearly any food will give rise to these symptoms. The fact that about eight hours pass before the onset of the symptoms, indicates that not the foodstuffs themselves but certain products of metabolism may be the causative agents in these cases.

Intolerance to foodstuffs has long been known and has been recognized by pædiatrists (Czerny, Feer, and others)

as a cause of many diseases of babies and children, but renewed interest has been centred on these matters since the discovery of anaphylaxis by Richet in 1902. As far as I know, Hutinel [27] was the first to draw attention to the relation of intolerance to foodstuffs and anaphylaxis, and since that time the subject has been studied extensively by many others. Recently Laroche, Richet, and St. Girons wrote an interesting monograph on " L'anaphylaxie alimentaire " in which also many cases from the older literature are cited.[28] They differentiate " la grande anaphylaxie alimentaire," " la petite anaphylaxie alimentaire," and a more chronic form of anaphylaxis. In " la grande anaphylaxie " the symptoms of hypersensitiveness are extremely serious; some cases of death in babies and grown-up persons after ingestion of very small amounts of egg, milk, or other foodstuffs are recorded in the literature. " La petite anaphylaxie " is much more frequent and the symptoms are less serious, consisting of conjunctivitis, eczema, intestinal troubles, rhinorrhœa, and attacks of asthma or of migraine. To this group belong the cases of Pagniez and Nast [29]—migraine only after eating chocolate; of Pagniez, Pasteur Vallery-Radot, and Haguenau [30]—asthma and urticaria only after eating crude egg-white, whereas boiled egg-white and egg-yolk were innocuous; of Laroche, Richet, and St. Girons [28]—intestinal disturbances after drinking cow's milk and not after drinking the milk of other animals, etc. It may again be remarked, that cases similar to those cited doubtless exist, but they are relatively rare. There is a large number of patients who show symptoms of allergy dependent on the intake of food, but for the most part an entire group, or groups, of foodstuffs is incriminated, and not only one substance.

Among the substances which are poorly tolerated by asthmatics foodstuffs containing uric acid compounds (i.e., meat, fish, and beans) take an important place. Sometimes ingestion of a certain kind of meat will immediately bring forth an allergic attack, which, then, is the demonstration of a specific hypersensitiveness. But apart from this, all uric-acid formers (meat, fish, etc.) will in many cases do harm, since they seem to increase the sensitiveness of the allergics. The result of investigations made by de Kleyn and the present author,[31] which were in accordance with experiments made by Lindemann [32] previously to ours, were in complete agreement with these clinical findings. We found that nearly all asthmatics show a disordered purin metabolism, i.e., the excretion of uric acid after a purin-rich meal, given during a period of purin-free diet (exogenous uric-acid excretion), is diminished. Lindemann had before us obtained exactly the same result; moreover, he showed that injection of uric acid could induce asthmatic attacks in a sufferer from asthma. Later, Heystek found in our institute that the concentration of uric acid in the blood of asthmatics is extremely low. In normal men twenty to thirty milligrammes per litre is a normal finding. In asthmatics we sometimes found a content as low as two and one-half mgrm., and the highest figure we found, viz., 12.5 mgrm., corresponds with the lowest figure found in normals (thirteen mgrm.).

We have sometimes noticed the occurrence of severe attacks of asthma in our patients after a purin-rich meal (thymus, or liver). Kämmerer [33] reports analogous observations made by Thannhauser. On the basis of these observations we hold the opinion that in most cases of allergy a purin-free diet should be prescribed.

There are other cases of allergy—not infrequently

seen—who do not tolerate carbohydrate foodstuffs and often they cannot stand milk and butter either; in these cases a diet of meat, vegetables, and small amounts of rice has to be given. The author tends to the view that here also the substances which have to be left out of the diet need not be allergens *per se,* but might only heighten the sensitiveness of the subject to other allergens which really cause his attacks.

5. HYPERSENSITIVENESS TO BACTERIAL PRODUCTS (BACTERIAL SENSITIZATION)

As far as I know Chandler Walker [34] was the first to ascribe sensitizing properties to bacterial proteins. Many asthmatics suffer from chronic bronchitis, and according to Walker a number of these patients become sensitized to the products of metabolism of bacteria which cause this bronchitis, so that each fresh absorption of these products gives rise to a new attack. This view has led to the introduction of autovaccines for the treatment of these cases of asthma, and the fact that such autovaccine treatment sometimes yields results has, by some authors, been considered a proof of the correctness of the theory. It cannot be denied that in some cases Walker's suggestion may be true, but in the majority of the cases of asthma accompanied by chronic bronchitis it certainly is not. In this respect we fully agree with Cooke's [35] criticism of Walker's view, viz., that the relation of asthmatic attacks to bacterial sensitization is unproved. The fact that autovaccine treatment gives relief of symptoms in some cases does not support in any way Walker's theory, since Cooke [35] and the present author [36] found that stock vaccines may yield exactly the same result, a fact recently demonstrated again in careful experiments by Rackemann and Graham.[37]

6. HYPERSENSITIVENESS TO COLLOIDAL SUBSTANCES OF UNKNOWN COMPOSITION, WHOSE PRESENCE IN THE AIR IS DUE TO CLIMATIC INFLUENCES (MIASMS)

On the basis of a careful study of more than 300 cases of asthma and other allergic diseases the present author has gained the opinion that although cases of hypersensitiveness, as described in the preceding sections, exist without any doubt, all these considerations are of little value for the great bulk of sufferers from asthma and other allergic diseases living in Holland, England, the north of Germany, many parts of America, tropical countries, and all regions with an analogous climate. In all low countries with a high humidity of the atmospheric air the majority of all allergics offer a peculiarity, known to every one, but the importance of which in relation to the etiology of the disease has been overlooked, viz., these patients suffer from their attacks only in certain places or in certain regions. The allergy is simply a disease of climate in these cases. Change of climate, if appropriately accomplished, stops all attacks within twenty-four hours, and they show themselves again only if the patient returns to his former place of residence.

Since the correctness of this view cannot be proved without having first discussed the " specific diagnosis " of allergic diseases the question of climatic factors will be deferred till a later section.

RELATION OF ALLERGY TO ANAPHYLACTIC SHOCK

Although a great number of new facts regarding hypersensitiveness and allergic diseases have come to our knowledge during the last ten years no satisfactory explanation of the mechanism of hypersensitiveness can as yet

be given. Still, a clearer insight in the matter would be obtained if it became possible to reduce the unknown mechanism to a phenomenon already known. Almost all endeavors to find an explanation, made during recent years, were based on this idea; in fact, the attempt was made to explain allergy on the basis of anaphylaxis. Since Richet discovered anaphylaxis in 1902 many authors have tried to bring the etiology of various diseases into relation with this phenomenon. A number of infectious diseases, eclampsia, sympathetic ophthalmia, serum disease, and many others, have been supposed to be manifestations of anaphylaxis. Among other things this has led to the erroneous use of the term anaphylaxis; some authors, for example, speak of serum sickness as true anaphylaxis. It is obvious that if an attempt has to be made to establish a relation between allergy and anaphylaxis, it will above and before all be necessary to designate clearly what is to be meant by the term anaphylaxis. It is proposed in this discussion to call anaphylaxis only the phenomenon originally described by Richet and Arthus, viz., a shock-like reaction induced in an animal by the second injection of a protein to which it had been previously sensitized, the same protein causing in an untreated animal no such shock-like reaction, or in any case a reaction of much less intensity.

Starting, then, from this basis, the question will be discussed whether allergic diseases are to be considered as manifestations of anaphylaxis in man.

If a " second " injection of an adequate amount of a protein, which has been injected into the same animal some weeks previously, be given intravenously to a guinea-pig, the animal will, after a short period of quietness, show signs of unrest; it will scratch itself as if suffering from pruritus, it will make violent masticating movements, it

will sneeze or cough a few times, and then suddenly it will show an attack of dyspnœa, eventually accompanied by violent convulsions. In the meantime fæces and urine are often voided, sometimes sperm is ejaculated, and after a short rest new convulsions may occur and the animal may die. If the thorax is opened at this moment, the lungs are not found collapsed as usually, but for the most part are inflated; there is a state of *volumen pulmonum auctum.* This condition, first observed by Auer and Lewis,[38] was ascribed by them to a constriction of the smooth musculature in the smaller bronchioles, an opinion which is still generally held. The conformity of these findings with those observed in bronchial asthma led to the view—first expressed by Meltzer—that bronchial asthma was a manifestation of anaphylactic shock in man, a view which was supported by the investigations of Schlecht and Schwenker,[39] who were able to show that in the alveoli of the lungs of guinea-pigs which had succumbed to anaphylactic shock, a marked eosinophilia was present, such as also occurs in bronchial asthma. Apart from the question whether this conception of the identity of both phenomena can be considered as strictly correct, it must be admitted that this theory has done much for the advancement of our knowledge of allergic diseases, as it has stimulated research and showed the direction in which investigation had to proceed. Almost simultaneously with Meltzer's explanation, Weichardt and Wolff-Eisner advocated the view that hay-fever is an anaphylactic phenomenon, and after that the same suggestion has been made for other allergic diseases. It must be remarked that already as early as 1908 Hutinel[40] had formulated the idea of "anaphylaxie alimentaire," referred to above.

When the theory of the anaphylactic origin of allergic diseases had reigned for some years and had gradually become accepted, great doubts arose as to its correctness. Although others have partaken in this debate, it has been mainly Coca [41] who combated the anaphylactic theory and who clearly formulated the arguments which prove against it.

It is superfluous to give a detailed review of all that can be said for and against Coca's standpoint, as the whole matter has been treated extensively and with great exactness by Doerr,[42] who also gives most extensive references to the literature on the subject. The present author has expressed his ideas on the matter on certain occasions [36] and until recently he has supported Coca's view. Subsequently, however, to new facts having recently been brought to light, he has been forced to change his position considerably, as will appear below.

The main arguments to be opposed against the anaphylactic theory are as follows:

1. Allergic diseases are often inherited, anaphylaxis is not.

2. Allergic symptoms are sometimes shown the very first time that a person comes into contact with the incriminated substance.

3. Allergy can only with difficulty and irregularly be induced experimentally in animals, anaphylaxis is easy to obtain in animals, whereas its existence in man has not been proved. Moreover allergics are not more readily sensitized to foreign proteins than normal men. Allergy cannot be transmitted passively to animals; in anaphylaxis this experiment usually succeeds.

4. The symptoms of allergy differ largely from those of anaphylactic shock, but show much likeness to those of

drug idiosyncrasy, whereas drug idiosyncrasy cannot be identical with anaphylaxis, since drugs are considered not to give rise to the formation of antibodies and consequently they are not anaphylactogens.

THESE POINTS HAVE TO BE CONSIDERED BRIEFLY

ad 1. All authors agree that in about fifty per cent. of cases the disposition to become allergic is inherited. In anaphylaxis hereditary factors play only an unimportant part. Rosenau has shown [43] that in animals anaphylactic sensitization can be inherited, but the sensitization is transmissible only by the mother and not by the father; moreover it is directed only against the same substance that served to sensitize the mother, and the sensitization of the young lasts a short time only. All these factors differ materially from those observed in allergy, since this condition is transmissible by the father as well as by the mother, it may be directed against various substances (a father may be sensitive to pollen, the child to horse dandruff), and it lasts a very long time.

Notwithstanding these facts Coca's argument seems not to be conclusive. It would be possible with regard to the fact that as a rule it is not the specific hypersensitiveness which is inherited—but only the disposition thereto—to admit the theory that nothing is inherited but an increased vulnerability of the skin and mucous membranes. This supposition, which has been proposed by Friedberger also, would remove all difficulties, since a great vulnerability of the skin and mucous membranes means big opportunity to become sensitized by foreign proteins, and it is clear that the *nature* of the protein or drug which sensitizes the child will often differ from that which sensitized the parent. It would also explain why,

in part of the cases, no hereditary factors exist, as many people will in later life suffer—chronically or temporarily (acute bronchitis, intestinal ulcers, eczemata!)—from increased vulnerability of the skin and mucous membranes. The observation of Cooke and van der Veer [44] that hereditary factors have most influence in cases which are sensitized during early life is in complete accordance with this supposition. Finally, the supposition that most asthmatics possess or have possessed an increased vulnerability of the skin or mucous membranes has been found by us to be correct. Of 150 asthmatics who were interrogated on this point fifty per cent. had suffered from the characteristic *Eczema faciei* in early childhood, whilst thirty per cent. had suffered from bronchitis prior to the onset of asthmatic symptoms. Of the remaining twenty per cent. some accused measles, typhoid, or intestinal ulcers, or operations on the stomach, occurring before the onset of the first signs of their allergic disease. Friedberger has studied a case in which hypersensitiveness to duck's eggs appeared directly after an intestinal operation.

In the face of these facts it is no longer possible to hold that the existence of hereditary factors excludes the correctness of the anaphylactic theory.

ad 2. On this point there is no doubt. Allergic symptoms may occur the very first time the person comes into contact with the allergen. This is against the anaphylactic theory, since the first sensitization is absent. The argument that serum sickness also occurs after a first injection is of no avail, as serum sickness appears only after a certain lapse of time after the injection, and, moreover, it is not proved that serum disease is of anaphylactic origin. It has been surmised that sensitization of the child is due to sensitization of the mother, but in that case the mother should

be sensitive to the same drug as the child, which is not the case. It has been supposed that during the period of lactation the mother might have eaten the allergic substance, which would have passed by means of the milk to the child. Indeed Shannon [45] has shown that protein, eaten by the mother, may pass into the milk, but this supposition is not sufficient to explain all the facts (hypersensitiveness to antipyrine, cases of allergy to pollen, etc.).

It must, then, be accepted that in *some* cases allergy exists without previous sensitization. In these cases the anaphylactic theory cannot be applied, but this does not imply that this theory would not be correct for the vast majority of allergic cases, where every possibility for sensitization has existed.

ad 3. Cases in which allergic diseases have been experimentally induced in animals have often been cited, but also the possibility of obtaining sensitization in animals by treating them with true allergens has often been denied. Friedberger [46] recently reviewed the literature on this question and brought forward experiments of his own which also proved the impossibility of obtaining experimental allergies. Guinea-pigs injected with extracts of horse dander and reinjected after a certain lapse of time with the same extract intravenously indeed showed symptoms of anaphylactic shock, but *inhalation* of this material did not cause anaphylactic or allergic symptoms even in animals sensitized by injection. Cooke, Flood, and Coca [47] also reported negative results; in our institute the attempt has been made on several occasions to induce allergic symptoms by forcing guinea-pigs to inspire dried horse serum or pollen. We experimented on animals sensitized by previous intraperitoneal injections and also on untreated animals; we gave daily inhalations, bringing the animals into a cage contain-

ing pollen or dried serum, or blowing the material into the animals' noses; sometimes we made a pause of two or three weeks and after that began again, but we were absolutely unsuccessful. In one series we had positive results; these animals, however, were ill and died soon afterwards. Contrary to these negative results, some authors are able to present positive ones. Koessler, Ulrich, Schloss, Curschmann,[48] and others succeeded in causing a state of sensitization in guinea-pigs by injecting them with the serum of allergic patients. Arloing [49] reports that sensitization by inhalations of allergens (pollen, for instance) is most successful in animals suffering from tuberculosis. Also in such animals he could induce anaphylactic symptoms by having them inhale pollen, dried serum, etc. This is in agreement with our results with sick animals reported above. The state of affairs, then, may be summarized as follows: if a guinea-pig is sensitized by *subcutaneous* injection of horse serum and afterwards is injected *intravenously* with the same material, as a rule shock ensues. But if the animal is sensitized by frequently blowing dried serum, or pollen, or horse dandruff, into the animal's nose and an attempt is made to obtain anaphylactic symptoms by the same procedure, the experiment will often fail and only certain cases give a positive result. The same may be said of passive sensitization. The injection of the blood of an anaphylactic animal into an untreated one will induce so-called passive anaphylaxis, but the injection of the blood of an allergic patient (asthma, hay-fever) into a guinea-pig does not regularly make the animal susceptible to a subsequent application of the allergen.

This has been considered to be an argument against the anaphylactic origin of allergy, and Coca even went further, as he stated that anaphylaxis does not occur at all in

human beings. According to him man can only become allergic. This opinion seemed to be strengthened by the fact elucidated by Cooke, Flood, and Coca,[50] that allergic patients are not more easily sensitized by subcutaneous injection of other allergens or anaphylactogens than normal people, while Landsteiner, Varekamp, and the author[51] showed that the natural sensitiveness of human beings to intracutaneous injections of various sera is only slightly greater in allergics than in normals.

For the present author the value of these arguments has decreased materially since a number of new facts have come to our knowledge. First there is no doubt now that anaphylaxis, caused by a primary injection of protein, really occurs in man; Doerr was able to gather a number of such cases. The argument that anaphylaxis is always passively transmissible to other animals, whereas allergy is often not, holds no longer, since we now know that anaphylaxis is not nearly always transmissible (transmission is possible only during the first weeks or months after the sensitizing injection), and that the possibility of transferring allergic sensitization passively to animals depends largely upon the moment chosen for the withdrawal of the blood of the allergic patient and upon the intensity of his state of sensitization. De Besche and Frugoni[52] have shown that immediately after an asthmatic attack, the patient's blood does not contain the substances which might transmit to animals or to men the susceptibility to the allergen, but after some time they seem to reappear.

The fact that the anaphylactic experiment succeeds easily in animals, whereas the allergic experiment often fails, does not, according to the author, disprove the identity of anaphylaxis and allergy. Anaphylaxis is an artificially induced phenomenon. *This* phenomenon (sensitiza-

tion by *injection,* shock by a second injection) occurs in animals and men, but allergy includes a sensitization by contact with the skin and mucous membranes, which as a rule befalls only human beings with a certain disposition. As has already been discussed above, one of the differences between the predisposed human being and the normal animal consists in the fact that the skin and mucous membranes of predisposed people are easily permeable to allergic substances, whereas the skin of normal animals is not. In this connection it is worth noticing that many so-called allergens contain a substance which is irritating to the skin or to the mucous membranes (ipecacuanha contains emetine, pollen often contains an irritating substance,[53] ricin is itself irritating, in Curschmann's cases a paraphenylenediamine preparation was present, etc.). In addition to this the whole question of anaphylaxis *versus* allergy has been cleared up considerably by a notable publication of one of Frugoni's co-workers, Ancona.[54] This author describes an epidemic of asthma among millers and peasants. The attacks of asthma accompanied by urticaria were caused by handling grain which had deteriorated to a marked degree and contained, among other parasites, a small insect, *Pediculoides ventricosus.* The point of interest is that practically everybody who handled this grain contracted a common skin disease, not of allergic or anaphylactic origin, while *all those who came into continuous contact with it* after some time developed symptoms of asthma and urticaria. In this case, then, the factor " predisposition " dropped out entirely. The deteriorating grain was irritating to the skin, and the diseased skin no longer offered a sufficient barrier to the allergic substance, which, after passing through the upper zones of the skin, sensitized the people and made them sensitive to subsequent

contact or inhalation. In this case nature has made the crucial experiment.

Still another difficulty has been cleared up by Frugoni. This author has proved beyond any doubt that the allergic state is transmissible from man to man.[52]

The first observation of this kind was made by Ramirez.[55] A man, who had up to that time never shown any sign of bronchial asthma, received a transfusion of blood. On leaving the hospital he appeared to have become hypersensitive to horse dandruff; inhalation of horse emanations caused asthmatic attacks. Afterwards it was found that the donor of the blood suffered from horse asthma. This fact seemed to prove the possibility of passive transmission of the allergic state. Coca, however, holds that the case is not entirely conclusive. According to him it is not proved that the patient who received the transfusion was not suffering from a latent predisposition to asthma, the blood transfusion might have acted as a non-specific stimulus; furthermore, the same donor also gave blood to other patients who did not become allergic. It cannot be denied that there is some truth in this criticism, but one of the cases communicated by Frugoni offers conclusive proof.

Frugoni injected sixty-eight c. c. of blood serum (two c. c. intramuscularly, ten minutes later one c. c. intravenously, and ten minutes later again sixty-five c. c. intravenously), derived from a case of marked hypersensitiveness to rabbit's hair, into a child of twelve years, who on previous examination had been shown to be free from any form of hypersensitiveness; skin reactions with various protein extracts were entirely negative. The donor of the serum was highly sensitive to rabbits. Skin reactions with extracts of rabbit's hair and also with rab-

bit's serum were positive. The child who had received the intravenous injection showed after twenty-four hours very strong skin reactions with extracts of rabbit's skin, reactions with extracts of rabbit's hair, and a marked reaction with rabbit's serum. The same day the child was asked to play with a rabbit, with the result that a typical " crise hémoclasique," as described by Widal, ensued; symptoms of irritation of the skin or mucous membranes were absent on that day, but were present when, two days later, the child was brought into the stable of the institute, where it again played with a rabbit. After twenty minutes, the child showed rhinorrhœa, itching in the nose and throat, hyperæmia of the conjunctivæ, lachrymation, coughing, and small urticarial wheals.

In view of this case it must be acknowledged that passive transmission of the allergic state from one human being to another human being is possible.

ad 4. Coca especially emphasizes the fact that the symptoms of allergy differ from those of anaphylaxis but show much agreement with those of drug idiosyncrasy. The view that non-protein drugs are not anaphylactogens is now generally accepted. According to him, both facts may be considered as an argument against the anaphylaxis theory. The first argument is not conclusive, as symptoms of anaphylaxis differ materially in different animal species, and they may also show variations in man according to the different sensitiveness of the various systems. Moreover, there is no reason why all anaphylactogens should induce exactly the same symptoms. It seems to me, then, that some variation in symptoms does not disprove the anaphylactic theory. The second statement, viz., the agreement between the symptoms of allergy and drug idiosyncrasy, is

doubtless true, but it may be explained in at least two ways without upsetting the anaphylactic theory.

As has been noted above, qualitative hypersensitiveness to drugs might be caused by the presence of the drug in the blood in a " free " state, the drug acting in this condition merely as an augmenter to other—allergic or anaphylactic —reactions proceeding, or latent, in the body.

A second explanation might be founded on the basis of the highly instructive researches made by Landsteiner.[56] This author has shown that it is possible to make artificial antigens by making compounds of proteins and substances of simple chemical constitution, for instance, atoxyl. If an animal is injected with a compound of serum albumin with a certain diazotized aromatic amino-acid, an immune serum is obtained which gives specific reactions with other proteins combined with the same amino-acid, whereas no reaction is obtained if the same albumin, in combination with another amino-acid, is used. In this case, then, the specificity of the reaction is no longer dependent on the albumin used, but on the aromatic group with which the albumin has combined. Landsteiner also found that not only *in vitro* but also *in vivo,* i.e., in experiments on anaphylaxis, similar results were obtained. It is obvious that, in view of these results, the possibility must be acknowledged that in drug idiosyncrasy the phenomena of hypersensitiveness are not only dependent on the drug introduced, but mainly on combinations of human protein with the drug, in which combinations the albumin would have lost its specific properties, the " drug " fraction deciding the nature of the specificity.

Considering all the facts described, one cannot but admit that the differences between anaphylaxis and allergy have become rather vague. Coca certainly goes too far in denying any relation between anaphylaxis and allergy,

since one cannot remain blind to the great similarity which exists between the two conditions.

Anaphylaxis has mainly been studied in animals, in which the proteins to be applied have, for the most part, been injected and sensitization has been obtained by one or two previous injections.

If in human beings foreign proteins are injected more than once, conditions exactly analogous to those of anaphylactic shock in animals may occur; in these cases, then, there is a complete agreement between anaphylaxis in man and in animals.

In allergic diseases the conditions are somewhat different. They may have been acquired not only by persons who possessed a certain inherited or acquired predisposition, but also by those who were quite normal before and showed no trace of predisposition. In these cases, however, sensitization to allergens occurs only after long-continued contact with these substances under conditions which facilitate their entrance into the skin or mucous membranes. These " facilitating conditions " are (*a*) a temporarily reduced resistance of the skin or mucous membranes (eczema, bronchitis, conjunctivitis, rhinitis, intestinal ulcer, intestinal operation, etc.), or (*b*) the presence of an irritating substance in, or adherent to, the allergens (emetine in ipecacuanha, ricin, histamine-like substances in pollen, paraphenylenediamine in Curschmann's cases). If both conditions are present, as in the cases of Ancona cited above (deteriorated grain), every human being is susceptible to allergic diseases. If the facilitating conditions are less marked only a certain number of people will acquire the disease. Finally, if a strong predisposition exists (extreme permeability of the skin and mucous membranes), non-irritating substances such as egg-white may

also give rise to allergic sensitizations. In all these cases the resemblance to animal anaphylaxis is striking, differences being easily explained by the fact that in animals sensitization is induced by injection, in man by continued contact. This conception being admitted, it is no longer astonishing that experiments in which sensitization by the inhalation of dried serum, pollen, or horse dandruff is attempted in animals often give no results, since the skin and mucous membranes of animals are not permeable to these proteins, nor on the other hand that sometimes positive results appear, as, for example, in Arloing's experiments on tuberculous animals and in our experiments with sick guinea-pigs, cited above. Furthermore, it is to be expected that if animal experiments are made with material containing irritating substances, positive results will also be obtained in normal animals. That such is indeed the case will be described extensively in a further section of this book.

All these observations do not annihilate the fact that hypersensitiveness to drugs or protein material is sometimes congenital. Certainly these cases are rare (although hereditary *predisposition* is frequent), but they doubtless exist. Keeping to the definition of anaphylaxis originally given, these cases cannot be considered as similar to anaphylaxis. This only proves that in the etiology of allergic diseases, there is at least one factor which we do not know. Nor is it certain that only one such unknown factor exists. Doubtless in cases of inherited predisposition, the vulnerability of the skin and mucous membranes (the existence of which has been demonstrated) must play a part. But it is far from certain that this explains the predisposition entirely. It may very well be that in persons with hereditary predisposition, the capacity for acquir-

ing immunization against foreign proteins is poorly developed, and besides there may be another internal factor which confers on them a tendency to become anaphylactic.

According to the author's present views, then (and somewhat in disagreement with views previously expressed), allergy and anaphylaxis have in many cases so much in common, that a study of the first phenomenon is impossible without due consideration of the second, while on the other hand a complete identification of the phenomena would be incorrect, as not being in accordance with the facts.

The author wishes it to be noted that this opinion on the relation of allergy and anaphylaxis is generally in agreement with the views of Doerr, as laid down in his recent review cited above.

SEARCH FOR CAUSATIVE AGENTS OF ALLERGIC ATTACKS

It goes without saying that as soon as it had been recognized that bronchial asthma, urticaria, etc., might be caused by hypersensitiveness to proteins or drugs, attempts were made to cure these diseases by methods analogous to those employed in hay-fever. After it had been found that these attempts were sometimes successful, the necessity arose of discovering the causative agent of every case of allergy, in order to be able to apply the specific treatment.

HAY-FEVER

The case of hay-fever was fairly clear. Speaking generally, the causative agent of this disease was known. Further work was required only to differentiate between cases caused by the inhalation of pollens of different plants. This differentiation may be made by means of skin reactions. If to a little scratch on the skin a small

amount of pollen is applied (with the addition of a drop of alkaline fluid), after a few minutes a wheal appears provided a pollen has been used to which the individual is hypersensitive. Intracutaneous injection of pollen extracts yields the same results. Normal people never show positive skin reactions with pollen extracts. Obviously a differential diagnosis of pollen hypersensitiveness may also be made by applying a small dose of pollen or pollen extract to the conjunctiva. This method is even more trustworthy than the first-named, since later investigations have shown that the reaction of the conjunctiva to several specimens of pollen is more specific than the reaction of the skin. Since, however, skin reactions are easier to apply and less troublesome for the patient, this method of diagnosis is generally chosen.

The number of different specimens of pollen which may produce hay-fever is conspicuous, but in most cases it is sufficient to apply only a small number of tests. Early hay-fever is mostly caused by the pollen of grass or one of the grains; of course differentiation between various pollens is necessary here, but it may be remarked that most of the early forms may be therapeutically influenced by applying small amounts of rye or timothy pollen; sometimes, however, we have to use other varieties.

For the later cases, pollens of some flowers are wanted and, of course, the choice of material is much wider here than in the early ones. Still, it is not necessary to determine skin reactions with all the specimens of pollen which have to be considered, since most patients are sensitive to more than one pollen, and often treatment with one pollen influences hypersensitiveness to other pollens also. Usually, applying tests with ragweed, golden-rod, chrysanthemum, dahlia, and aster will suffice. In rare cases a

more specific diagnosis may be needed and a larger number of pollens must then be tested. The publications of Cooke and van der Veer should be consulted, as they have determined the pollens which are liable to cause hay-fever in the United States.

CAUSATIVE AGENTS OF ASTHMA AND OTHER ALLERGIC DISEASES

Conditions are much more complicated in the case of asthma and other diseases. While some few cases of asthma are caused by inhalation of pollen, making the diagnosis easy, in most cases considerable difficulty arises. The present author even holds the opinion that in the majority of cases of asthma the real causative agent cannot be found at all, but for the sake of simplicity he will postpone the discussion of this point of view until later, and indicate first how, according to the views of many competent workers in this field, a specific diagnosis may be made.

According to current opinions four groups of asthmatics come into consideration:

Group I contains those patients who are sensitive to horse dandruff, rabbit's hair, goose feathers, etc. They constitute the group of hypersensitiveness to "animal proteins."

Group II consists of those hypersensitive to foodstuffs, eggs, milk, pork, strawberries, etc.

Group III contains cases of "bacterial sensitization," and

Group IV holds a small number of cases of hypersensitiveness to drugs.

It is obvious—although it is often forgotten—that before other methods of diagnosis are applied, a careful interrogation of the patient should be made. Sometimes

this will reveal useful facts. The patient may have observed that he always gets attacks in a certain room, in a certain house, or in a certain place. Moreover, it should be ascertained whether the patient comes in frequent contact with horses, dogs, cats, and other animals; he should be asked of what sort of stuffs the material of his bed is made (mattress of horsehair, pillows of feathers!), and what kind of foodstuffs he is accustomed to take, etc. Sometimes the cause of asthmatic attacks will be discovered in this way, at other times merely an indication for a possible cause will be obtained. Generally, however, this interrogation will tell us next to nothing. Recently the author studied eighty cases of asthma in a rural district from an etiological point of view; most of the patients came in daily contact with ten different animals, they were used to eating about thirty different foodstuffs, and they all inhaled the odors of several kinds of dung-yards. Examination of the composition of their beds showed that each bed consisted of at least ten different materials (feathers, horsehair, capoc, wool, flax, etc.), and although peasants in this country are considered to be very clean, any amount of "house dust" could be found in every house. Indeed, a considerable amount of imagination was needed to be able to find the etiological factor of the asthmatic attacks in a single one of these cases.

As verbal examination mostly fails, resort must be had to other methods.

SKIN REACTIONS IN ASTHMATICS

If an asthmatic is very sensitive to horse dandruff or other proteins, his skin will usually react to the application of this substance. This peculiarity of the skin has been used to find etiological factors in asthma. Technically

the skin test can be applied in two ways, viz., the skin-scarification test and the intradermal reaction.

Skin-scarification tests were initiated by Schloss and brought into general use by the work of Chandler Walker. The technique is very simple; Walker describes it as follows:

" A number of small cuts, each about an eighth of an inch long, are made on the flexor surfaces of the forearm. These cuts are made with a sharp scalpel, but are not deep enough to draw blood, although they do penetrate the skin. On each cut is placed a protein and to it is added a drop of tenth normal sodium hydroxide solution to dissolve the protein and to permit of its rapid absorption. At the end of a half-hour the proteins are washed off and the reactions are noted, always comparing the inoculated cuts with normal controls on which no protein was placed. A positive reaction consists of a raised white elevation or urticarial wheal surrounding the cut. The smallest reaction that we call positive must measure 0.5 cm. in diameter."

Small vials containing material for the application of these tests can be obtained from some manufacturers. Instead of dry material, fluid—so-called protein—extracts of animal dandruff, foodstuffs, etc., may also be used. These extracts may be purchased in the open market, though many investigators prefer to prepare them themselves, the preparation being a relatively simple procedure. The rough material is cut into small pieces, treated with ether, extracted with alkaline fluid, and sterilized by filtration through a Berkefeld or Chamberland filter. We have during the last years always used extracts prepared in our own institute.

For the intradermal reactions various dilutions of these so-called protein extracts are used. Usually 0.1 to 0.01

c. c. of fluid is injected into the skin with a fine needle. This injection nearly always produces a small wheal which disappears after fifteen to thirty minutes if inactive material is injected. In a case of hypersensitiveness of the skin the wheal becomes larger and persists longer than that caused by a control injection with simple saline solution. Since these skin reactions are by no means free from danger, due care must be taken to use the proper dilutions of the protein extracts for these tests. Some manufacturers offer "solutions for diagnostic injections" and separate "treatment sets" of various proteins.

NUMBER OF TESTS TO BE APPLIED

The number of tests which may be applied is practically unlimited. Nearly any foodstuff may be considered as a possible cause of hypersensitiveness, and the same may be said of nearly any animal hair, bed material, or constituent of house dust. Some investigators use eighty protein extracts, others go further and use 120, many content themselves with thirty or forty. The present author and his co-workers have found that if forty extracts are used, including some animal proteins, some foodstuffs of different types (meat, fish, vegetables, fruit, etc.), some bed materials, and some specimens of house dust, positive reactions may be obtained in every asthmatic. Some investigators use also extracts of bacterial proteins; this point has already been discussed above.

VALUE OF THE SKIN TESTS IN RELATION TO THE ETIOLOGICAL FACTORS OF ALLERGIC DISEASES

Is it possible to detect the causative agents of allergic attacks by means of skin reactions? This is the dominating point of the entire problem under discussion and, consequently, it will have to be considered most critically.

If, in the way described, intradermal skin tests are made with 0.1 c. c. of various dilutions of forty to eighty protein extracts, positive reactions will be found in nearly all cases. Indeed, the trouble is—and as far as I can see on this point everybody is agreed—that usually a great number of positive reactions are found, sometimes thirty or more in one patient. Since, in such cases, the result of the cutaneous tests gives little information as to the identity of the causative agent of allergic attacks, means have been sought to make the reaction more specific. Two solutions of this problem have been proposed; Chandler Walker omits the intradermal tests and applies scarifications only, Cooke, Coca, and their co-workers keep to intradermal injections but dilute their solutions and inject smaller amounts of fluid (0.01 or 0.02 c. c.).

Walker's method gives far fewer positive reactions than the others. It is very difficult to state what percentage of cases of asthma will show a positive reaction with the scarification method. Walker gets positive reactions with some type of protein in forty-eight per cent. of cases.

The present author, using dry material, obtained only a few positive reactions with scarification tests in fifty asthmatics tested. We tend to the view that cases showing specific skin reactions are relatively rarer in Holland than in some other countries. Recently Roth from Korany's clinic (Budapest) tested a small number of asthmatics with about ten foodstuffs, using the scarification method, and obtained many more positive reactions than we did. During the last year—in consequence of researches made by Frugoni, Ancona, and ourselves—we have started to apply skin tests not only with the extracts described, but also with extracts of material infected with various insects or micro-organ-

isms, and in this way we have obtained also with the *cutaneous* tests many more positive reactions than we formerly did.

Cooke recently published his results with both methods. He also finds too few positive reactions with Walker's method and holds that intracutaneous tests give better results. As has been pointed out above, the intradermal method has been abandoned by Walker and others because it gives too many positive reactions. Cooke criticizes this view; according to him the intradermal test gives too many reactions only if 0.1 c. c. of the various protein extracts is injected. He injects 0.01 to 0.02 c. c. and gets better results. It appears to the present author that Cooke's criticism is unsound. It goes without saying that injection of a large amount of an active solution will as a rule cause a larger wheal than injection of a smaller amount of the same fluid, and consequently injections of 0.1 c. c. will give more reactions than injections of 0.01 c. c. *But this procedure does not make the method more trustworthy.*

In order to be able to appreciate the truth of this statement it is necessary to realize that the extracts used for intradermal tests form a material of wholly uncontrollable strength. As has been briefly stated, protein extracts are made by extracting a certain amount of protein material (horse dandruff, rabbit's hair, meat, egg-white, etc.) with a certain amount of weak alkali. It must not be forgotten that nobody has the slightest idea of the nature of the active substances contained in these extracts, their chemical composition being entirely unknown. It is possible that the active substances are proteins, but even this point has never been proved. This state of affairs makes it utterly impossible to standardize these protein

extracts. Cooke and others have tried to get an approximate standardization by determination of the nitrogen content of the extracts. It is clear that this method might give a slight indication if the strengths of two extracts from the same rough material were to be compared, but the method is useless if the strength of an extract of horse dandruff has to be compared with that of an extract of goose feathers. It is well to emphasize this point, since it forms the basis of every discussion on the value of intradermal skin tests.

Even if it were proved that the active substance of the so-called protein extracts were indeed of protein nature, nitrogen determinations would give no information about the amount of it, as the main mass of protein in a certain extract may be totally inactive. We have often had in our hands extremely active protein extracts, in which not even the presence of protein could be demonstrated by qualitative methods. On the other hand, there exist extracts with high nitrogen values and low specific action. It must not be forgotten that the strength of a protein extract is much less dependent on the quantity of nitrogen contained in it than on the degree of sensitization of the patient. Without exaggeration it may be stated that, of two extracts containing the same percentage of nitrogen, one may be a thousand times more active than the other.

If chemical standardization of these extracts is impossible, cannot they be standardized physiologically? This also is impossible and for a very simple reason. Protein extracts are active only in allergic patients, they have no " normal " action. Of two extracts, one may be a hundred times more active if tested on the asthmatic A, while the other may be much more active if tested on the asthmatic B.

IS THERE, THEN, NO CRITERION FOR THE STRENGTH OF PROTEIN EXTRACTS?

According to the writer's view, only one criterion can be applied. These extracts—if used intradermally—serve to indicate a difference between the behavior of the skin of normal people and that of allergics. The strength of the extracts, then, should be such that they never give a positive reaction in a normal man. Another restriction should be made; the extracts must be so diluted that they are harmless to the patient who has to be tested.

The arguments offered obviously lead to the conclusion that in cases where several positive reactions are found with injections of 0.1 c. c. of fluid, there is no possibility of determining which reaction indicates the causative agent of the asthmatic attacks. Reduction of the quantity of fluid injected to 0.01 c. c. may reduce the number of positive reactions, but, since the strength of the extract is unknown, it does not make the test more " specific," and it only makes the diagnosis more incomplete.

Skin reactions may teach us in what respect an allergic patient differs from the normal, and, if the trouble of making a great number of injections is taken at all, it is wise to make the diagnosis as complete as possible; hence the quantity of fluid injected should not be reduced too far, and the only restriction which must be rigidly observed is *that the extracts in the dilution used and in the quantity injected give negative reactions in normal people.*

The question now arises, what indications do positive skin reactions give with regard to the causative agent of allergic attacks?

The author and his co-workers have studied this matter very carefully and with as much accuracy as possible, and have come to the conclusion that the causative agent of

allergic attacks is seldom revealed by skin reactions. We tested sixty-two allergic patients and thirty-six normal people with cutaneous and intradermal injections of twenty to fifty protein extracts. The extracts had been made according to the indications published by Cooke. We found that nearly all asthmatics reacted to intradermal injections of more than one extract; thirty-seven per cent. of our cases reacted to more than ten extracts, fourteen and one-half per cent. to from five to nine, and twenty-six per cent. to from two to five extracts. The fact that a great percentage of asthmatics give positive reactions to more than five extracts, when only twenty to fifty extracts are tested, indicates that more positive reactions would be found if more extracts were tried. It would not be difficult to bring the number of protein extracts up to 200.

Apart from this there is another fact which has often been overlooked, namely, that the quantity of animal protein present in the respired air is totally unknown. Who would be able to give even a rough estimate of the quantity of horse dandruff, goose feathers, and rabbit's hair in the air of Holland or the United States? A patient may show an extremely high skin sensitiveness to rabbit's hair and a weak reaction to cat's hair; what indication as to the causative agent would this give if, perchance, the general air contains ten thousand times more cat's hair than rabbit's hair? Who knows whether even a breeder of rabbits ever inhaled a quantity of the specific protein of rabbit's hair sufficient to cause an attack of asthma?

The fact that some persons suffer from asthmatic attacks when they come into the vicinity of horses is undeniable. It is possible, although unproved, that these attacks are caused by the inhalation of horse dandruff. These patients give positive skin reactions to horse dan-

druff—and eventually to a number of other proteins—but this does not prove that any one who shows positive intradermal skin reactions to horse dandruff suffers from "horse asthma." Cases of so-called "horse asthma" are very rare, but cases which give a positive intradermal skin reaction to extracts of horse dandruff are extremely frequent, viz., sixty-seven per cent. of all our cases tested.

A similar criticism can be applied to the case of positive reactions to extracts of foodstuffs. True cases of specific hypersensitiveness to *one* foodstuff are very rare; in 200 asthmatics I found only one case of true hypersensitiveness to eggs, but positive skin reactions to egg will be obtained in a greater number.

THE REAL IMPORTANCE OF SKIN REACTIONS

Although the present writer is forced to deny the usefulness of intradermal reactions as a method for finding the causative agent of allergic attacks, he still holds the view that the inauguration of these reactions in the diagnosis of allergic diseases has been an important step. All allergics give one or more positive skin reactions, whereas normal people do not. *Intradermal* skin reactions may serve to diagnose *the allergic state, but not to make a specific diagnosis.*

Although all allergics show one or more positive reactions, each allergic reacts to different proteins. This would necessitate the use of a great number of extracts in order to be able to make the diagnosis of an allergic state. Recently, however, the author and his co-workers found that there exists one protein extract which gives positive reactions in practically all cases of allergy. Curiously enough, this is the extract of "human dandruff."

This fact is of some importance. In cases of asthma,

the diagnosis of "allergic state" is for the most part simple enough; but in cases of urticaria, eczema, and other skin diseases, and especially in cases of migraine, it is often extremely difficult to determine the presence of allergic disease. In these cases a diagnostic injection of the extract of human dandruff may be very useful.

It is not yet possible to give a satisfactory explanation of the relation between allergic diseases and positive skin reactions to human dandruff. The reaction is to a large degree "specific," i.e., nearly all allergics react, normal people almost never.* Human dandruff almost always contains a large number of bacteria and of spores of fungi; it is not impossible that products of bacteria or fungi produce the skin reaction, as is possible for all animal protein extracts. This point is being investigated in our institute at the present moment. Apart from this it is well to realize that the fact that all asthmatics show positive skin reactions to human dandruff greatly strengthens the author's view as to the worthlessness of *intradermal* skin reactions as a means of making a *specific* diagnosis.

DIAGNOSIS OF ALLERGIC DISEASES. CONCLUSIONS

As will be discussed later on, adequate treatment in allergic disease can be applied even if the causative agent is unknown. It is, however, absolutely necessary to be sure whether the patient suffers from an allergic disease or not. This information can, if the case is not yet clear, be

*It should be stated that not all extracts of human dandruff are suitable for use. Sometimes these extracts contain a substance which produces positive reactions in normal people too. This substance can generally be eliminated by ultrafiltration, since it passes through a collodion membrane which holds back the "specific" substance of the extract. Sometimes the ultrafiltrations must be repeated. In a few instances it has been impossible to purify the extract, in which case it was rejected.

obtained by making one single intracutaneous injection of an extract of human dandruff, together with one control injection of physiological saline. If the fact that an allergic disease is present has been established a search for a specific diagnosis is necessary. First *cutaneous* tests have to be applied; in the case of hay-fever they will usually settle the question, but in asthma and other allergic diseases they will often fail, although in a number of cases they may give very useful information. If all cutaneous tests are negative, the possibility that *intra*cutaneous tests may reveal the cause of the attacks is small, but it may be tried. In that case the extracts should be used in dilutions and in quantities which do not produce positive reactions in normal people. It is wise to make the choice of dilutions and quantities such that as complete as possible a diagnosis is obtained. It is very important to know that doubtless cases of allergy exist which *give negative skin reactions (cutaneous and intracutaneous) with an extract of the allergen which causes the attacks. General* reactions with these allergens may be obtained by intracutaneous or subcutaneous application.

EXTRACTS OF HOUSE DUST

It is a known fact that many asthmatics suffer more from attacks in one place than in other places; even certain houses are worse for them than other houses. The reason for this strange peculiarity was, until recently, wholly unknown. Then Cooke and his co-workers made an important observation which may offer the clue to this problem. They gathered dust from the floor of " asthma houses," made " protein extracts " of this dust, tested the extracts in asthmatics and found that a large percentage of them gave positive skin reactions with house-dust ex-

tract. They even obtained general reactions with these extracts. Cooke was not able to identify house-dust extract with any one of the known protein extracts. We can confirm Cooke's observation completely. Extracts of the dust gathered from several houses produced positive skin reactions in a number of normal people and in a greater number of asthmatics. In two cases intracutaneous injection of very small amounts of house-dust extract into patients suffering from severe attacks of asthma caused violent attacks—indeed, in one it provoked a *status asthmaticus* during eight hours—though, curiously enough, the *skin* reaction was negative in this case. The quantity injected contained less than 1/1000 milligramme of nitrogen, and two hundred times this dose was inactive in normal mice. The fact that normal house dust contains a substance which may induce attacks in an asthmatic must be considered as very important. The first step to be taken must be the determination of the nature of this substance.

WIDAL'S CRISE HÉMOCLASIQUE OR COLLOIDOCLASIQUE

About the same time as in America and other countries diagnostic cutaneous methods were first applied, Widal and his co-workers worked out another method. They found that under certain conditions in the animal body a " rupture " of the equilibrium of the blood occurs, giving rise to four main phenomena:

(1) Lowering of blood-pressure; (2) drop of leucocytic count; (3) change of refractometric index of the blood; and (4) change in clotting time.

One of the conditions which bring about this " rupture " presents itself if an allergen is introduced into the body of a sufferer of an allergic disease. Thus if a hay-

fever patient inhales pollen, a *" crisis "* will follow, or if a person hypersensitive to quinine takes a dose of the drug he will show a *" crisis,"* etc. After their first publication Widal and his co-workers stated that in order to make the diagnosis of a *crise colloidoclasique,* it was not necessary to determine all four signs of a *crise,* but instead, a single count of the number of leucocytes would suffice. The present author, together with his co-workers, observed, however, a fact which has been confirmed by others, that the finding of a drop in the leucocytic count is certainly not sufficient to make a diagnosis of a *crise colloidoclasique.* Consequently, all investigations on the *crise colloidoclasique* in which only leucocytic counts are made are of little value. If one wants to use the phenomenon of *crise colloidoclasique* in work on allergic patients, it is necessary to determine the whole set of signs originally described by Widal. The author fears that even after doing so, the fact that following application of a certain material a *crise* is found, does not give a trustworthy indication as to the importance of this material in connection with the occurrence of allergic attacks. If with the same material normal people do *not* give a reaction, the finding of a " crise hémoclasique " proves that the individual under observation is hypersensitive. Hence the value of the finding of " crise hémoclasique " is about equal to the value of a positive skin reaction.

DANGERS OF SKIN REACTIONS

It should be remembered that intracutaneous skin reactions are not free from danger. All workers in this field agree that in a certain percentage of cases " general reactions " will ensue after an intracutaneous test. These " general reactions " may consist of urticaria, asthmatic

attacks, syncope, collapse, etc. Apart from this, the author and his co-workers have repeatedly observed that allergic patients, although not showing definite "general reactions," have complained of an exaggeration of their symptoms during the first two or three weeks following application of a number of diagnostic tests.

Cooke has published a case in which diagnostic injections of an extremely small quantity of a fish extract (containing about 0.002 milligramme of nitrogen) caused death in a child suffering from very serious bronchial asthma.* We have seen two cases with very serious symptoms after diagnostic injections. Theoretically, mishaps like these can be avoided, since an innocuous dose of every protein extract can be found. Since, however, the susceptibilities of two asthmatics to a certain extract may differ by 10,000 times or more, it is practically impossible to avoid severe reactions if a large number of protein extracts are tested. In the author's institute it has been made a fixed rule that the *first* intracutaneous injection in any patient shall always be preceded by a scarification test with the same substance. The intracutaneous injection is allowed only if the cutaneous is negative.

While we hope in this way to avoid serious reactions, moderate general reactions or an increase in the symptoms cannot be avoided. This has led us to abandon intracutaneous skin reactions, with the exception of injections of human dandruff, as a routine method in allergic patients and to keep them only for definite purposes. This step we adopted with little hesitation, since we had formed the

* This emphasizes the fact related above, that a positive skin reaction with a certain allergen does not prove that this allergen is the cause of the allergic attacks. The child in Cooke's case certainly showed an extremely high sensitiveness to this particular fish, but this fish could not be the cause of her asthma!

impression that in many cases the treatment of allergic diseases could be effected efficiently without them.

INFLUENCE OF CLIMATIC FACTORS ON ALLERGIC DISEASES; THE AUTHOR'S MIASM THEORY

During the course of investigations on the significance of diagnostic skin tests in allergic patients, the author and his co-workers have been impressed by the fact that although positive reactions will be found in practically all our cases of asthma, it was relatively seldom possible to incriminate one of the known allergens as the causative agent of the attacks.

Before entering further into this question, one point must be emphasized, viz., the discrepancy between the relative number of cases of typical allergy, i.e., due to known allergens, found by authors of different countries.

Walker in America finds forty-eight per cent. of cases due to known factors, Cooke in the same country gives still higher figures, while Frugoni in Italy finds ten positive reactions in thirty-two cases tested. Roth in Budapest, in testing thirty asthmatics, finds ten positive cases. Widal in France holds the opinion that true " anaphylactic " cases of asthma are rare, and, as has been stated above, in the author's institute the positive cases were even extremely rare (five or six in 300 cases).

Part of these discrepancies may be due to differences in the technique used or to differences of interpretation, but it is unlikely that this would explain the matter entirely. It seems to the author to be undeniable that among a hundred asthmatics taken at random in Italy or Hungary there are many more " typical " cases than among a hundred asthmatics in Holland. Since the considerations to be given below hold for the " atypical " cases

only, the fact must be borne in mind that the importance of the matter to be discussed will vary for different countries. It will be most important for Holland, north Germany, many regions in England and America, and for many tropical countries. For other countries the importance will be less, but still there will be hardly any country for which the observations about to be made will not hold at all.

The starting-point of the author's theory was the observation that a great number of asthmatics and other allergic patients suffer more from their attacks in one place than in another. This fact is known by every one who treats allergic patients, but the importance of the fact in relation to etiology seems not to have been recognized. In some instances the influence of " place " may be easily explained by the occurrence or absence of the known allergens. If an allergic patient suffers from attacks caused by the inhalation of dog emanations, he will be free of attacks in all places where dogs are absent, but this kind of explanation covers only the minority of cases. In the great majority of cases no reasonable explanation, founded on the occurrence of known allergens, is to be found; to cite a definite example: an asthmatic suffers very much in Rotterdam but never in the Hague, although the distance between the towns is only twenty kilometres. It is known that a great number of asthmatics do better at the North Sea coast than in the country, but dogs, horses, cats, rabbits, and goose feathers are as frequent in seacoast villages as in other places.

Early in our research work on allergic diseases, we realized that the occurrence of these diseases seemed to differ widely in different regions of our country, small though it is. Since the outcome of our investigations in

this direction is not only of local interest but may throw a new light on the etiology of allergic diseases *generally,* this point will have to be discussed fully.

The following were the first facts relative to factors of "place" which impressed us. (1) Nearly all patients who were sent to us from Zeeland (a province consisting mainly of islands in the southwest of the country) showed this peculiarity, that, as they told us, they suffered badly from attacks at home (a fact corroborated by letters from their physicians), but never showed any sign of an attack in Leyde. Skin tests revealed the occurrence of many reactions of hypersensitiveness, but a specific cause for their attacks could never be determined. Treatment gave very poor results.

(2) Rotterdam seemed to offer a much greater contribution to our allergic cases than other cities, and we were struck by the fact that these cases also did less well than those from the Hague.

These two facts, together with the observation that even our most difficult cases lost their attacks at once in certain places in Switzerland (a fact already described by others), induced us to study the question of allergy from a different point of view, viz., to make an investigation of climatic factors.

As we had the impression that the island group of Zeeland produced our worst cases, whereas certain regions in Switzerland are practically free from asthma, we felt that comparative researches between the conditions in Zeeland and Switzerland had to be made. Accordingly we made many excursions to Zeeland and one to Switzerland. The results of researches made during these visits have to be briefly discussed, as they offered the clue for the explanation of the matter.

BRONCHIAL ASTHMA IN ZEELAND

The population of the islands of Zeeland consists of a peculiar and beautiful race, which differs considerably from the other Dutch population. The people are dark, have finely cut faces, and are intelligent. Tuberculosis is rather frequent, psychoses also (nearly always of a melancholic tendency), and the death-rate among the newly born children is high, although the economical position is favorable.

For our studies on asthma we chose one of the larger islands (Zuid Beveland) but excluded the principal town of the island, as only in rural villages can trustworthy information on the number and the location of asthma cases be obtained. By the kindness of Doctor Folmer and many colleagues, we were able to get a complete survey of all the cases on the island (except in the town mentioned and one small region).

Briefly stated, we found the following points of interest. Among approximately 35,000 inhabitants about eighty cases of asthma could be gathered; this makes more than two cases per thousand inhabitants. As the number of cases amongst the population of other regions is not known—as far as the author is aware—the figures given do not at present offer convincing evidence that asthma is extremely frequent on this island. As may, however, be seen from the accompanying chart (Fig. 1), the distribution of cases over the island is not equal. In the south of the island we found villages in which *from one-half to one per cent. of the population* suffered from asthma. This, then, proves that asthma is indeed extremely frequent in these places. We furthermore noticed that in the western part of the island, in a region extending one km. north and one km. south of the railway, eight cases of asthma were

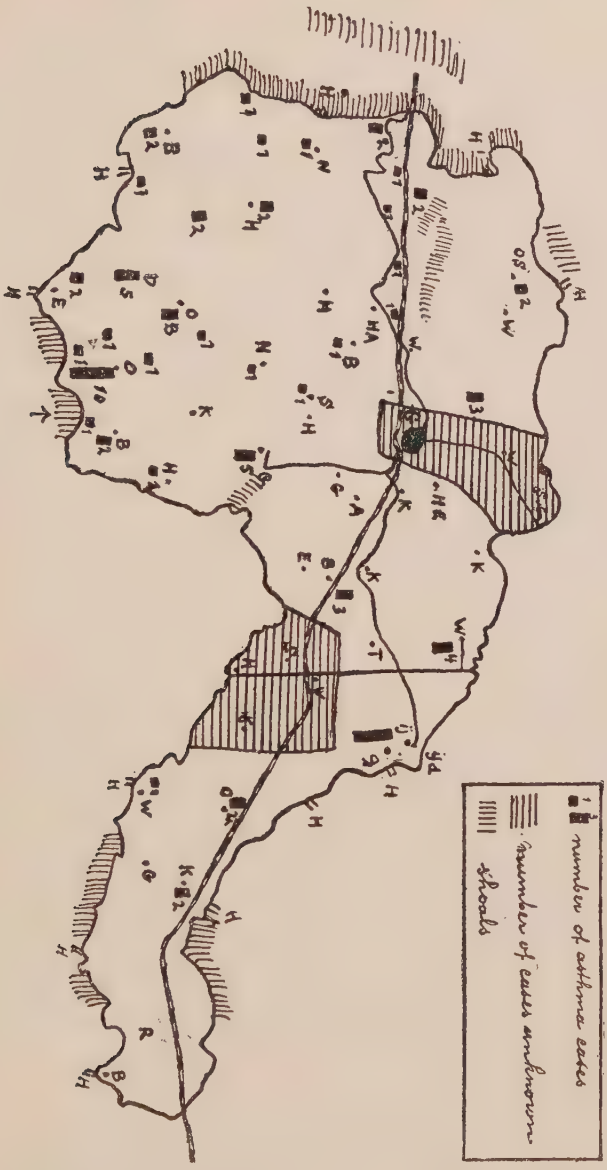

FIG. 1.

present, whereas certainly less than a hundred houses are situated in this region. The cause of this extreme frequency of asthma is not known. We only noticed that all centres of asthma are situated in the vicinities of shoals (Dutch: schor), which are for the most part found on the seaward side of the dykes which surround the island. To the north of the railway mentioned above, a shoal is also present. These shoals are always extremely moist, they are often covered with sea-water and contain a flora, and consequently a micro-flora, which differs entirely from the flora found elsewhere in the country. In this connection it is worth noticing that in one house situated on the landward side of a dyke, but very close to it (and consequently also close to the shoal which lies on the other side), within twenty years, three people from different families showed their first signs of asthma. There are on the island two houses similarly situated; in both one of the occupants is asthmatic.

Another possible explanation for the frequency of asthma on this island might be found in the circumstance that a great quantity of wheat is raised on these islands and that, in distinction to other districts, it is the custom for every farmer to keep the quantity of wheat necessary for a whole year in his house. This wheat always contains large numbers of mites during the summer, and consequently the inhabitants have the products of wheat infected with mites in their close vicinity during the entire year. It may be remembered that we found that grain under such circumstances always contains allergens. (See below.)

It might be surmised that the tuberculous or psychopathic predisposition of these islanders might be the real cause of their tendency to asthma. This, however, is

unlikely, and the chances are greater that the reverse is true, and that the same cause which induces asthma also induces psychopathia. As a matter of fact we have noticed that the inhabitants of this island seldom have attacks of asthma outside of Zeeland. Of twenty-four cases which had at some time left the island, twenty told us that they were much better or absolutely free from attacks as soon as they left this region. Of the remaining four, none had ever been in foreign countries, so that the possibility exists that they also belong to the same group.

The following case is illustrative. A woman whom we visited told us spontaneously that both her sons, who suffer from asthma, and who usually sail in Rhine boats, always lose their attacks as soon as they enter Germany as far as Cologne, and that their attacks always reappear after coming home. These facts prove with certainty that the cause of the asthmatic attacks is not an inherent factor of the population, but of the country. They furthermore prove that the known allergenic factors, such as horse dandruff, cat's hair, dog's hair, goose feathers, also the common foodstuffs and bacterial sensitization, are not of deciding importance in these cases. The asthmatic attacks are due to substances present in the air, the nature of which is unknown, but the occurrence of which is certainly due to peculiar climatic factors (in a broad sense) existing on these islands. These substances may be indicated—by a name frequently in use in the period before Pasteur—as *miasms.*

ASTHMA IN SWITZERLAND

During the summer of 1923 we made an excursion to Switzerland with three Dutch asthmatics whose cases we had been able to study for many months before we started

for our trip. All three belonged to a type which is frequent in this country; asthmatics of this type, on every occasion on which they are examined, always show slight asthmatic signs, râles and whistling sounds; in addition to these they also suffer from severe attacks. In two of these patients (F and B) attacks were known to be very dependent on the circumstance of " place," F being a typical case of Zeeland asthma. Acute attacks in the third patient (K) are due to the inhalation of dust from grain infected with mites, probably also to other causes.

Five places in Switzerland of different heights were visited, viz., Basel (150 m.), Ragaz (800 m.), Vulpera (1200 m.), Davos (1500 m.), St. Moritz (1800 m.). We stayed for three days in each place and the patients were examined daily. The result was quite clear. In Ragaz F and B showed some improvement, K was unchanged. In Vulpera F and B were decidedly much better, K unchanged. In St. Moritz (1800 m.) *all three patients were without any signs of asthma or bronchitis,* a condition which, until that time, had not occurred for years. In Davos their conditions were about the same, but slightly worse. On returning to Holland, all three patients got severe attacks within twenty-four hours.

Three patients, then, two of whom were typical cases of asthma due to climate (whereas in the third case it was uncertain whether climate had an influence), lost their signs of asthma within twenty-four hours after arrival in St. Moritz. The attacks came back after returning to lower places. F has since that time stayed in France at a height of about 1300 m., where he is always quite well, but as soon as he returns to lower regions the attacks reappear after some days.

These facts are in complete accordance with observa-

tions on many other patients, and with those of physicians in Vulpera, St. Moritz, and other mountain villages.

Turban stated that above 1500 or 1800 m. practically no asthma occurs, that about sixty-eight per cent. of all asthmatics who come to these places are completely free from attacks and twenty-five per cent. very much relieved within a very short time after arrival.

The question arises as to why these asthmatics are free from attacks in some places, but suffer so much in others. The fact that such great differences exist between places in Holland which are as close together as the Hague and Rotterdam (22 km.) or the Hague and Zeeland (70 km.) excludes the possibility that temperature, atmospheric pressure, and humidity of the air play an important part, although these factors may have an additional influence.

It seemed to us that two possibilities existed. It might be that in the mountains a substance is present in the air which prevents the occurrence of asthmatic attacks (in the same way as the smoke of asthma cigarettes does), or it might be that a substance which causes attacks in lower regions is absent from the mountain air. The latter possibility would be in accordance with our conception of asthma, as due to the inhalation of miasms.

In order to test the probability of the two possibilities we made the following experiments. In St. Moritz K was absolutely without asthmatic signs. We made him sit down in a bathroom, with the upper part of his body uncovered. Auscultation revealed the absence of râles. We put into his hands a box of oats containing mites, which he had brought along from his own farm for this purpose. This box he held under his nose, and shook from time to time so that some dust appeared; after three minutes he sneezed violently, and after eight minutes he

had marked signs of bronchial spasm, while his breast and shoulders were entirely covered with small urticarial wheals. The signs of asthma stayed for twenty-four hours. Two days later, in Davos, the patient being in perfect condition, we repeated the experiment with the same result.

These experiments prove that at altitudes of 1500 and 1800 m. our asthmatic patient suffered from asthma only if one of the substances to which he is sensitive was present in the air.

ANIMAL EXPERIMENTS WITH SUBSTANCES WHOSE OCCURRENCE IS DUE TO CLIMATIC INFLUENCES

In order to ascertain whether the conditions which, according to our views, prevail in man in certain climates may also be induced experimentally in animals, we made the following experiments.

Guinea-pigs were placed without any previous treatment in cages, on the bottom of which oats or wheat infected with mites was spread. This material had been sterilized to avoid the possibility that the living mites would *per se* disturb the animals. In most of the investigations groups of five animals were placed in the cage for three hours, and this procedure was repeated daily or with intervals of some days.

The behavior of the animals in the cage is interesting.

The first day most of the animals will show slight symptoms of distress, but apart from these they will behave normally; one or two, however, will, after some minutes, become restless; they will scratch themselves violently, they will frequently sneeze and make chewing movements; alternately with these symptoms they will during ten or fifteen minutes sit quietly in a corner of the

cage, and show more or less intense dyspnœa. The next day the symptoms of all these animals will be more intense, and perhaps one of the others also will show some signs; certainly after three or four days *all* the animals will show the signs described, in a greater or lesser degree. The intensity of the symptoms will increase and after a period of some weeks will decrease, till finally a condition is reached in which the animals are only slightly disturbed by the inhalation of this material. If the experiment is continued, however, every now and then an animal will again be affected; subsequently it will behave normally again; then show some symptoms a few days later, and so on. During this period most of the animals will have lost in weight, and some of them will have died. Death may occur in two ways; sometimes the animal becomes ill and suffers from bronchopneumonia due to infection with some bacteria. If, during this illness, it is placed in the cage, its dyspnœa will increase considerably and it may die in convulsions within an hour. But sometimes also an animal, apparently in good health, will suddenly, after being in the cage for some time, show violent dyspnœa of asthmatic type, convulsions and lowering of temperature to thirty degrees or thirty-three degrees C., and subsequently will die within an hour. In three such cases postmortem examination revealed only extreme congestion of the lungs, while cultures of blood taken from the heart, and from the lungs and liver, remained completely sterile.

If during a period of marked symptoms, the animals are injected intracutaneously with 0.05 c. c. of an extract of the allergic material (oats with mites), they will for the most part show general symptoms of slight shock (scratching, sneezing, etc.): of six guinea-pigs tested in this way one showed severe symptoms, three marked symptoms, one

slight symptoms, and one none. Four untreated animals remained absolutely normal after this injection.

In a former chapter the difficulties encountered in inducing experimentally allergic symptoms in animals were explained, and it was emphasized that experiments with the known and common allergic substances, although sometimes successful, do not give regular results. With the substance used in our experiments positive results were obtained in every one of more than forty guinea-pigs and four rabbits tried. We also found that very young animals (8–20 days old) behave like adults, with the exception that they will for the most part show symptoms on their first contact with the substances; some will not, but will show them after two or three days.

Results analogous to those described, but less intense, could be obtained with other material, viz., oats infected with fungi. We are convinced that among the substances which cause allergic diseases of climatic type, fungi, or rather products of fungi and yeast, are prevalent. One of the arguments which strengthen this opinion is that in those places in Switzerland where our patients were most well, two types of fungi, which are always to be found in the air in our regions, viz., *Penicillium glaucum* and specimens of *Aspergillus*, and also yeast, were completely absent from the atmospheric air.

We infected larger quantities of moistened oatmeal with *Aspergillus fumigatus* (which occurs on grain in this country) or with *Penicillium glaucum*. After some weeks the material was dried and sterilized and the experiments reported above were repeated with it. It appeared to be active, although less intense than the grain containing mites, used above. It may be mentioned that the material infected with *Aspergillus fumigatus* was more active than

that infected with *Penicillium*. Of fifteen animals exposed to this material five died. One animal died three hours after its first contact with the material; it was found in convulsions, with a temperature of thirty degrees C. Cultures taken after its death from the lung, liver, and heart's blood remained sterile. Two animals died with symptoms of dyspnœa of asthmatic type, and two seemed to suffer from bronchopneumonia. Nearly all these animals lost in weight during these experiments, although they were kept under conditions in which untreated controls did extremely well.

To sum up, it may be stated that our experiments show that symptoms of rhinitis and conjunctivitis, pruritus, and dyspnœa of asthmatic and other types, and even death with symptoms which resemble considerably those of anaphylactic shock, may ensue in untreated guinea-pigs after the first or a subsequent contact with substances present in the houses and barns of the greater part of the rural population in regions where a climate similar to that of Holland prevails. It must be remembered, however, that the substances used in these experiments are only examples of allergens due to climate. It is not at all sure, nor even probable, that they must be considered the "real" miasmatic substances of these countries.

ETIOLOGY OF BRONCHIAL ASTHMA

The author intends to propose a theory which may help to produce a better understanding of the etiology of bronchial asthma and other allergic diseases. But before doing so, he is forced to touch on one other question. Why do some people acquire allergic diseases, whereas others exposed to the same allergic substance do not? This question need be discussed only briefly, since the main arguments concerning it have been surveyed in a former chapter.

There is no doubt but that many asthmatics have inherited a predisposition for acquiring allergic diseases. All authors agree that the number of allergic patients showing hereditary factors amounts to about fifty per cent. On the other hand, it is beyond question that people of completely normal disposition may also, by sufficiently long contact with allergens, acquire allergic diseases. The observations of Ancona on epidemic asthma leave no doubt on this point.

We tend to the view that one of the main factors of hereditary and other predispositions consists of an increased permeability or vulnerability of the skin and mucous membranes. As has been mentioned above, we have in fact found that fifty per cent. of our asthmatics have suffered in childhood from a peculiar form of *Eczema faciei*, while thirty per cent. have suffered from bronchitis prior to the onset of the asthmatic attacks. Of the remaining twenty per cent., some had passed through a period in which the intestinal wall was certainly more permeable than normal (typhoid, gastric ulcer, etc.).

Starting from these facts and using as a basis the other arguments and the experiments related above, the following conception of the etiology of allergic diseases is offered.

Allergic diseases are caused by the inhalation or ingestion of substances which are toxic for the patient. These substances may be toxic in the first instance or they may be purely allergens, i.e., only active after sensitization.

Normal people are not susceptible to the action of the pure allergens, but they may under certain circumstances become sensitized. This sensitization may take place by injection, as in the case of serum treatment or blood transfusion (Ramirez's case), but may also be induced by prolonged contact with the allergens, if other irritating substances are present so as to make the skin or mucous membranes more permeable. The most prominent examples of this possibility are the cases of epidemic asthma described by Ancona, some of Curschmann's cases (asthma due to fur dyed with paraphenylenediamine), cases of ipecacuanha asthma (in which emetine might act as the irritating substance), and also cases where allergic diseases manifest themselves after intestinal ulcer or intestinal operation.

Predisposed people (including the hereditary cases) will become sensitized to allergens even if the irritating substance has only a weak action or is entirely absent. Most of these people have suffered from illnesses which make the skin or mucous membranes more permeable (*Eczema faciei,* bronchitis), consequently sensitization is in this way made easier. Irritating substances will be more irritating for them than for normal people; this is another reason for their becoming more easily sensitized.

The following point is of interest.

If a child suffers from *Eczema faciei* many proteins occurring in the air will be enabled to pass through the skin, and having once accomplished this, they may sensitize the child. According to the kind of proteins prevailing in the air the child will become sensitized to horse dander, rabbit's hair, etc. But if the child lives in a country where the unknown substances mentioned above and called "miasms" are always present in the air, *it cannot but be sensitized to these substances also.* This explains why in these countries pure cases of single sensitization are so rare. The factor of climate always plays an additional part.

It must not be forgotten, that it is not possible to draw a sharp line between irritating substances and the so-called true allergens. The substances occurring in grain infected with mites and in grain infected with some fungi are certainly allergens, because animals and human beings who tolerate these substances on first contact gradually become sensitized. But these substances may certainly have a primary irritating action, since eight-day-old guinea-pigs (from a non-sensitized mother) may show definite symptoms on their first contact with them. And it is easy to understand that those people whose mucous membranes are more permeable than normal suffer more from the primary action of these substances. In many cases these allergens must be compared, not with anaphylactogens like egg-white, but with toxins. They have a primary toxic action, but they are *also* allergic.

Another question is: what happens if allergens pass through the skin or mucous membranes?

There are two possibilities: the individual will be sensitized or he will become immunized.

In our animal experiments we regularly observed both

processes to occur alternately. Some animals are insusceptible at their first contact, but after some days they become sensitized and some weeks later immunized; afterwards other periods of sensitization may follow. Some animals are sensitive at their first contact; this sensitiveness increases, but subsequently decreases and may be followed by another period of sensitization and immunization. A few animals do not become immunized; their symptoms increase and they die.

Very likely the same processes occur in man, but usually on a more modest scale. Most people become immunized, a few do not and become sufferers of allergic disease; some may even die of it.

This means that the supposition of increased vulnerability of the skin and mucous membranes (a supposition which has been proved to be the condition actually existing) does not suffice to explain the etiology of allergic diseases. It explains how allergens may enter into the circulation of allergics; it does *not* explain why the allergic individual does not become immunized, whereas many other people do. Consequently it is necessary to assume a lack of immunizing power in the body of allergics. That many allergics also show a deficiency in the defending mechanism against abnormal (idiosyncratic) actions of drugs, has already been pointed out above. This deficiency of a defending mechanism may go so far that proteins, completely innocuous for normal people, may be harmful; these are the cases of congenital hypersensitiveness to egg-white, cow's milk, etc.

As far as I am aware, this conception, which assumes the presence of two factors, viz., increased permeability of the skin and mucous membranes and deficiency of immu-

nizing power, explains all the known facts relating to allergy. Moreover it has been shown by the writer that the first factor occurs in most cases of allergy, while the second one has been proved to be present in some cases of drug hypersensitiveness. Although the occurrence of both factors may be necessary to explain certain cases of allergy, the observations of Ancona (epidemic asthma among normal people) prove that the first factor—vulnerability of the skin—may be sufficient.

* * *

In the preceding section almost all our attention has been centred on the specific causes of allergic attacks, and only occasionally have non-specific factors been mentioned. It is well, however, to remember that by the search for specific factors the problem is by no means exhausted. There is another side of the question, viz., why are certain people so easily sensitized?

Some points relating to this have already been emphasized above. In this connection the author wants, however, to draw attention to a research made some years ago by Zeydner and himself.[53] We found that if blood of an asthmatic patient is drawn from a vein (under certain precautions described in our original paper, and which must be adhered to carefully) and received in ten volumes of ninety-six per cent. alcohol, so as to induce coagulation before clotting has set in, the fluid obtained will contain a poison, which, after evaporation of the alcohol, will show a stimulating action on the smooth muscles of isolated organs. Normal blood if taken under exactly the same condition does not yield this poison.

These facts are illustrated by Figs. 2, 3, and 4. Brabant in a recent publication [87] stated that he was unable to corroborate our results. He found that human blood

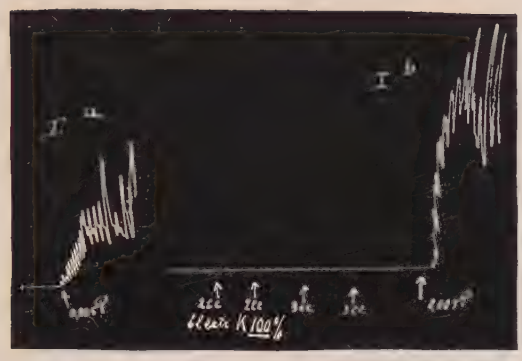

FIG. 2.—Extract of normal blood has no influence on isolated gut. *a*. 0.005 mgrm. pilocarpine hydrochloride added to 75 c. c. tyrode solution gives moderate contraction of gut. *b*. 10 c. c. blood extract corresponding to 10 c. c. blood from normal man gives no contraction; 0.005 mgrm. pilocarpine subsequently given produces strong contraction.

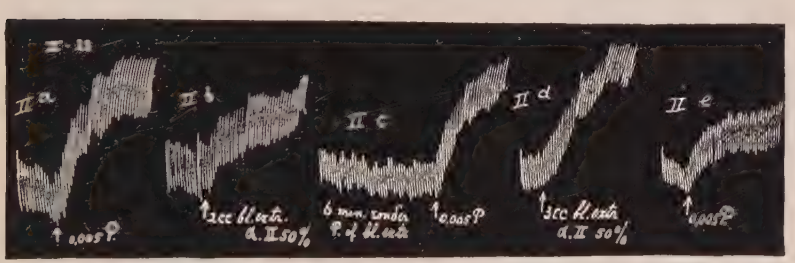

FIG. 3.—Influence of blood extract from severe case of asthma on isolated gut. *a*. 0.005 mgrm. pilocarpine gives moderate contraction. *b*. 2 c. c. blood extract corresponding to 1 c. c. blood gives contraction of gut. *c*. Action of 0.005 mgrm. pilocarpine. *d*. Action of 3 c. c. blood extract corresponding to 1½ c. c. blood. *e*. Action of 0.005 mgrm. pilocarpine.

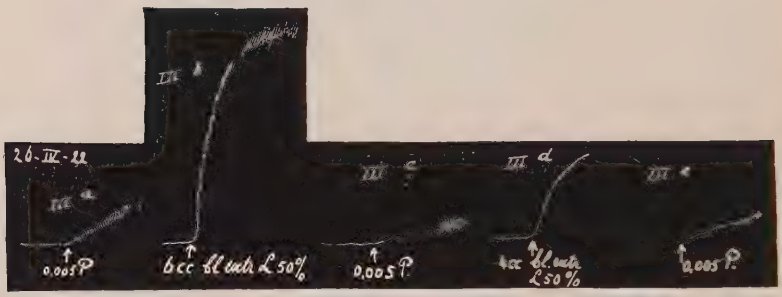

FIG. 4.—Action of blood extract from a severe case of urticaria. *a*. Action of 0.005 mgrm. pilocarpine. *b*. Action of 6 c. c. blood extract corresponding to 3 c. c. blood. *c*. Action of 0.005 mgrm. pilocarpine. *d*. Action of 4 c. c. blood extract corresponding to 2 c. c. blood. *e*. Action of 0.005 mgrm. pilocarpine.

received in alcohol always contains substances which stimulate the smooth muscle of the isolated intestine and he could not find any difference between the blood of asthmatics and the blood of normal men. Zeydner and the present author have since our last publication examined blood extracts of more than forty allergics and of more than twenty normals. All asthmatics were positive; all normals or non-allergic patients except one (suffering from nephritis) were negative. The fact that Brabant found positive reactions with normal blood as well as with blood from allergics suggests that his technique was not sufficient to detect the differences found by us. It is known that *every* sample of blood will after clotting contain substances stimulating smooth musculature; it is entirely unnecessary to put the blood in alcohol in order to obtain this reaction. As has been stated clearly in our first paper,[53] the finding of differences between normal blood and blood of allergics could only be anticipated after Freund and Gottlieb [82] had shown that under certain particular conditions blood of a *normal* person—if allowed to run directly from the vein into a glass containing ninety-six per cent. alcohol—does *not* contain the known "clotting" substances.

Subsequently we found that blood of allergics drawn under exactly the same conditions yields a substance stimulating the isolated intestine.

How far this fact will make it possible to explain the heightened sensitiveness of allergics to several agents cannot yet be judged.

THERAPY OF ALLERGIC DISEASES

Since allergic diseases for the most part manifest themselves as " attacks," separated by periods of complete well-being, it is necessary to discuss two phases of therapy, viz., the treatment of the acute attack and the treatment of the disease as such. The first task, treatment of the individual attack, is the easier one by far; the second is much more difficult.

TREATMENT OF ACUTE ATTACKS OF BRONCHIAL ASTHMA

Large numbers of drugs and methods to cut short asthmatic attacks have been advised. It is not necessary to give a survey of all these, since there is one drug superior to all others and this is adrenalin. If properly applied, adrenalin will in very rare cases only fail to prevent severe attacks. Many physicians inject adrenalin only if the attack has already reached its acme. This is wrong. If adrenalin is to be used, it should be given as soon as the first symptoms of a coming attack show themselves. The doses necessary will then almost always be much lower than the dose which is generally given: 0.2 to 0.4 c. c. of the common 1/1000 solution of adrenalin will as a rule suffice.

The best way of application is the subcutaneous injection. Given by mouth, it has very little or no action. The proposition that adrenalin should be given at the onset of an attack implies that in all cases in which sufferers from bronchial asthma are treated outside of the clinic, the injections will have to be administered by the patient himself or by one of his relatives, as the physician will nearly always come too late. Many physicians dislike

seeing the syringe in the patient's hands, but according to the author's view there is no other possibility. Moreover, there is not much danger in it. Our experience has taught us that few people are so unintelligent as to make it impossible to teach them the proper handling of the syringe. We have seen hundreds of patients who had frequently given themselves injections, and in only two cases was there an indication of an infection caused by imperfect asepsis. It must not be forgotten that the chance of an infection with virulent cocci is less great in a private house than in a clinic. Apart from the danger of infection there is the danger that the patient will misuse his syringe and inject himself too often. This danger really exists, but it is not greater than with any other medicament which will cut short the attacks. We have often seen patients who smoked asthma cigarettes day and night in unlimited number, and we have known others who " burned " asthma powder nearly every hour.

The author's opinion on this matter may be expressed as follows:

Every drug which is continually taken may do harm to the patient, but on the other hand it is not at all good for the patient's health to have asthmatic attacks for many hours, days, or even weeks. Serious sequelæ, such as bronchitis or bronchopneumonia, and, as late complications, emphysema, deformation of the thorax, heart disease, etc., may result. So of two evils the least harmful must be chosen, and this is adrenalin. Moreover, if adrenalin is not given the patient will take some other drug. He might be induced not to do so but for the fact that he will, by frequently being unable to work, lose or imperil his position, or see his affairs go wrong.

Fully acknowledging, then, that it would be better if no drug at all were necessary, we feel that we are obliged to allow sensible and trustworthy patients to give themselves adrenalin injections (or to have them administered by a relative).

How much adrenalin is to be given?

Although we often inject into our patients admitted to the hospital larger doses, we never allow our outside patients to give more than 0.4 c. c. per injection, and we always urge them to take the smallest dose that will be effective. This dose may be given three times or—in exceptional cases—four times daily. In hospital cases we often have to give larger and more frequent doses, but our experience has taught us that for outside patients a dose of 0.2 or 0.3 c. c. (or as a maximum 0.4 c. c.) given three or four times a day must be considered the limit. These quantities will be well tolerated for a very long time; besides, during this time everything possible will be tried to effect a real cure of the disease, so that further injections become unnecessary.

Relative to the size of the dose of adrenalin to be administered, it may be remarked that every patient will, if once his attention is drawn to it, do his utmost to cut down the quantity to be injected as far as possible, for the simple reason that, when more adrenalin is injected than is strictly necessary at that particular moment, untoward symptoms will always result. After an injection of adrenalin, many people feel sick and shaky, and suffer from tremors. This condition lasts for ten minutes, a quarter of an hour, or sometimes longer; but we have often noticed that asthmatics very seldom suffer from these symptoms if the dose injected was just as much as had to

be given at that moment. For example, an asthmatic will tolerate very easily 1 c. c. of adrenalin if he is in the middle of a severe attack, but some days later, if the attack is only very slight, 0.4 c. c. may cause very disagreeable symptoms. During the application of the therapeutic measures to be discussed in the next section, it is often noticed that the first sign of the change in the patient's condition is his announcement that a dose of adrenalin which did him no harm before now makes him feel uncomfortable.

This fact, together with the circumstance, that the sensitiveness of asthmatics to adrenalin changes very little even after long-continued use of the drug (apart from change in sensitiveness due to change in severity of the asthmatic attacks, as related above), shows that adrenalin is not to be considered as a habit-forming drug. Doubtless people exist who take too much adrenalin, but they always take it because they suffer from attacks; as soon as the attacks cease, the application of adrenalin is also stopped. I have never seen a patient who took adrenalin without being dyspnœic. There exists no " craving " for this drug, as there is for morphine, cocaine, etc.

Besides adrenalin, a large number of other drugs is in use; in certain cases atropine may be useful, but it has the disadvantage of sometimes making the condition worse. Some people are hypersensitive to atropine. Yet we sometimes give it, and then usually in large doses of three or four milligrammes daily, in cases where adrenalin injections are not possible, or for special reasons are undesirable.

Caffeine applied subcutaneously may be of some use in those rare cases in which adrenalin fails to reduce violent asthmatic attacks. We then often insert some injections of from 100 to 200 milligrammes of caffeine.

Apart from this, all other drugs are inferior to adrenalin; they may sometimes have an action, but if adrenalin fails they will fail also.

There is, however, a further exception to this rule. Morphine and chloral hydrate may in some cases stop asthmatic attacks, even when adrenalin has been shown to be useless, but these cases are extremely rare, and since the danger of cultivating drug habits is extremely great in asthmatics, the use of morphine, chloral hydrate, and similar drugs in the treatment of asthmatic attacks should be abandoned.

Treatment of attacks of other allergic diseases does not differ materially from that of asthmatic attacks. In all cases adrenalin is the most efficient drug. Violent attacks of urticaria, for example, often disappear in a few minutes after injection of 0.5 c. c. of adrenalin.

THERAPY OF THE ALLERGIC CONDITION

In those cases of allergy in which the causative agent of the attacks is known, two methods of therapy are available, viz., the specific and the non-specific. If the specific agent is not known—which condition, as has been pointed out above, occurs as a rule—non-specific treatment only can be applied.

The principles on which both methods, the specific and the non-specific, are founded, are the same, so that it is advisable to discuss these principles, viz., antianaphylaxis and skeptophylaxis, first.

ANTIANAPHYLAXIS

If a guinea-pig which has been sensitized by a previous injection of a certain protein is reinjected—not sooner than a fortnight later—with the same protein, it will show

a series of symptoms, violent dyspnœa, convulsions, etc., known as anaphylactic shock. The outbreak of these anaphylactic symptoms may be prevented by using a method first described by Otto and later by Besredka.[57] This method consists of desensitizing the animal by the injection of several doses of the protein (the antigen), beginning with very minute quantities and gradually and slowly increasing the dose. In this way the animal is brought into a state of antianaphylaxis. There is no use in entering deeply into the theoretical side of this problem, but it is necessary to emphasize the fact that antianaphylaxis is not identical with immunity; one of the differences is that the antianaphylactic state can be induced in an animal in a very short time, viz., in one or two hours, whereas immunity can only be brought about in the course of some weeks. The antianaphylactic state, once induced, does not persist; it passes away in the course of some weeks.

SKEPTOPHYLAXIS

We have seen that antianaphylaxis protects the animal for some weeks; skeptophylaxis, however, offers protection only during some hours. As early as 1880, Albertoni[58] showed that the toxic effects of large intravenous doses of peptone in animals can be prevented by a previous injection of a small dose of the same toxic substance. Afterwards Fano[59] and Gley and Le Bas[60] confirmed his statement and extended it to other poisons. In 1911 Lambert, Ancel and Bouin,[61] working with extracts of organs, showed that in this case also the phenomenon exists. As far as I know, they were the first to introduce the name skeptophylaxis; nowadays the same name is often used to designate a method of treatment which consists of giving

a patient a small dose of a poison, or foodstuff, a short time before a larger quantity, which might produce allergic symptoms, has to be given.

The phenomenon of skeptophylaxis, then, was first demonstrated with peptone (perhaps the method was already in use previously in cases of drug idiosyncrasy), and peptone was injected to prevent the effects of a subsequent injection of the same substance, but later it appeared that peptone may also serve to prevent the onset of anaphylactic symptoms due to other substances. This has led to a more wide-spread use of skeptophylactic therapy with peptone; the use of the method was still further increased when French investigators showed that peptone taken *per os* might also prevent anaphylactic symptoms.

Pagniez and Pasteur Vallery-Radot [62] administered peptone *per os* in cases of "*anaphylaxie alimentaire*" (urticaria, migraine); Widal and his co-workers gave it in bronchial asthma. Auld [63] gave subcutaneous and intravenous peptone injections in asthmatics. Joltrain [64] again administered it by mouth and Cordier [65] *per rectum*. The technique and results of this method will be discussed later.

It is probable that other methods of treatment of allergic diseases, such as milk injections (used by Weil in "*anaphylaxie alimentaire*" in infants), and injections of sulphur and auto-serum, will have to be considered as related to skeptophylaxis, although there are certainly differences also. The last-mentioned method, called autohæmotherapy, was, so far as I know, introduced by Ravaut [66] and by Achard and Flandin.[67]

Skeptophylactic therapy in drug idiosyncrasy is applied in two ways. Sometimes an attempt is made to

desensitize the patient by giving him very small but gradually increasing daily doses of the drug; in this case the method resembles more the antianaphylactic treatment. Often, however, the real skeptophylactic method is used. The patient is induced to take a very small dose of the drug one hour before taking the efficient dose. Often the last is then well tolerated.

The skeptophylactic treatment of drug idiosyncrasy is not new, but owing to the work of the French investigators, renewed interest has been taken in it. Thus, one of the cases described by Widal and his co-workers [68] has become very well known. It was a case of hypersensitiveness to antipyrine, which could be sensitized and desensitized (by skeptophylaxis) at will.

The essential part of skeptophylaxis, as has been described above, is that it gives only a temporary protection. Pagniez and Nast [69] describe a case of hypersensitiveness to chocolate in a man who tolerates chocolate quite well if he has taken some peptone previously. This condition has already existed for years, but if he omits the peptone, chocolate will cause severe symptoms of allergy. There are, however, other cases in which, after long-continued application of the therapy, the hypersensitiveness gradually disappears.

It is known that the production of anaphylatoxin *in vitro* may be inhibited by the addition of salt. Sicard and Paraf [70] first applied this form of skeptophylaxis by giving injections of bicarbonate solutions in order to prevent salvarsan or serum shock. Widal gave large quantities of NaCl solution in cases of asthma; later other salts and also hypertonic solutions of glucose were given in similar cases.

SPECIFIC TREATMENT

All methods of specific treatment of allergic diseases are based on the same principle, viz., the injection of a very small quantity of the allergen may prevent the outbreak of attacks caused by that allergen. Thus if a hay-fever patient during the season of his attacks is injected with a small quantity of pollen, his symptoms will decrease in intensity or disappear entirely during the first three or four days. If, then, a second injection is made, a further free period of three or four days can be obtained. And the same holds good for injections with other allergens in cases of hypersensitiveness to horse dander, rabbit hair, etc. The dose of allergen to be injected in this way has to be chosen very carefully, as too high a dose may bring about an allergic attack. If a series of injections is made in this way, one often notices that the sensitiveness of the patient to the allergen gradually decreases. Although the first dose may have caused a slight reddening and swelling at the site of injection, later doses may fail to do so; at the same time the general sensitiveness of the patient may be decreased; consequently the dose may be increased without doing the patient harm. This reduction of sensitivity of the patient is an additional and valuable consequence of the therapeutic injections.

If, in the way described, a series of injections with gradually increasing doses of the allergen has been given, the sensitiveness of the patient will sometimes have been reduced so far that the quantity of allergen which may come in contact with him (through inhalation in the air, in his food, or in any other way) is insufficient to induce attacks in him. He may then be considered as cured, although his condition of hypersensitiveness certainly has

not disappeared entirely. Intracutaneous injections of allergen will still produce a wheal, although it may be smaller than formerly. If large quantities of allergen are injected or if an abnormally great amount of allergen occurs in the air he respires, he will still show an allergic attack, although it will be less intense than before. The patient has not been brought into a state which can be compared altogether with antianaphylaxis, nor has he been immunized; his state of allergy has simply been lowered so far that he has become capable of normal life.

Cooke and van der Veer [71] and Freeman [72] discuss this point in relation to hay-fever. During a period of pollen treatment in cases of this disease, the sensitiveness of the conjunctiva and also of the skin will decrease, but some months after the treatment has been stopped, the conjunctiva will regain its former sensitiveness. During the next hay-fever season pollen treatment must be applied again, the only difference being that therapy is easier this time. If treatment during this year is omitted, the chances are that the patient will the following year be in the same state of hypersensitiveness as he was before treatment was started. It must be mentioned, however, that some cases are on record in which, after one season's treatment, a complete and lasting cure was obtained.

From this account the possibilities and the limitations of antiallergic specific therapy will be clear. Almost always will it be possible, by applying specific treatment, to lower the patient's sensitiveness to a certain degree, but it depends on the intensity of his former hypersensitiveness and on the quantity of allergen with which the patient usually comes into contact, how far this " lowering of his sensitiveness " will be of any help to him. That anti-

allergic therapy includes not only therapeutical injections but also the withdrawal, if possible, of the allergen from the patient's vicinity goes without saying. To this description of the specific antiallergic treatment one important point has to be added. Subcutaneous injections of allergen given to an allergic patient may not only reduce his sensitiveness but may also sometimes heighten it. This may occur if too high doses are used. The heightened sensitiveness may last for some weeks and sometimes be so pronounced that a dangerous situation ensues. It is obvious that the greatest chance of doing harm lies in the first therapeutical dose given. This danger of inducing heightened sensitiveness is one of the drawbacks of specific antiallergic treatment.

The following is an instructive instance of such a case. On March 30, 1923, an apothecary suffering very much from so-called ipecac-asthma applied to us for treatment. This was a very typical case. Formerly he had tolerated ipecac quite well, but after a period of two years, during which he had worked in a shop where large amounts of ipecac were handled, he had gradually become sensitized to the drug, and to such an extent that attacks of asthma set in even if Dover's powder was prepared in a room next to the one in which he does his own work. He never has any sign of asthma if he does not come into the vicinity of ipecac.

On testing the sensitiveness of the skin, the patient showed positive reactions to intracutaneous injections of dilutions of 1/10 milliard of ipecac, whereas positive reactions with emetine were only obtained with a dilution of 1/10,000, so that this was a case of hypersensitiveness to another water-soluble substance present in ipecac (presum-

ably of colloidal character). From April 5 to September 5 the patient was treated with subcutaneous injections of various dilutions of ipecac, starting with 0.1 c. c. of 1/10 milliard and reaching 1 c. c. of 1/10,000. During the treatment the patient's hypersensitiveness was reduced so far that he was able to stay in the room where ipecac was handled, and he could even touch the drug himself. His skin reaction was positive with a dilution of 1/10,000,000 at that period, whereas the therapeutical injection administered subcutaneously had in only one or two instances produced a local reaction. Hoping to obtain a complete desensitization, the treatment was continued with higher concentrations; when, however, dilutions of 1/1000 were reached, the patient complained of renewed attacks after handling ipecac, and as long as these high doses were given his condition grew worse, so that we were forced materially to decrease the dose to be injected. Here, then, is a clear-cut case of a typical hypersensitiveness to one allergen only. Consequently this case should be expected to show no difficulty at all in treatment, and yet after having given injections during nineteen weeks, and although the quantities injected were very carefully chosen, a renewed sensitization set in. The case is illustrative, as it shows how great an amount of difficulty may be encountered in cases where the causative agent of the disease is *not* known or where multiple sensitization exists.

TECHNIQUE OF SPECIFIC TREATMENT

The main difficulty of specific treatment lies in the selection of the first dose. If the first dose is too high, it may be followed by disagreeable symptoms. If it is too

small, it is inactive. Most authors make their choice as follows: a series of intracutaneous injections with varying dilutions of the allergen is made, and the dose which just fails to give a positive reaction (or the dose which just gives a slight reaction) is taken for the first subcutaneous injection. This method is reliable in hay-fever; in other allergies, however, it does not avoid all difficulties.

(1) The intracutaneous injections may themselves give general reactions in the patient.

(2) There is no definite relation between the effect of an intracutaneous and of a subcutaneous injection of the same substance.

I have seen cases of asthma where subcutaneous injection of an allergen in a quantity a hundred times smaller than an amount which had not caused a positive skin reaction produced severe symptoms.

For these reasons the present writer, in all cases except hay-fever, prefers another method. He always gives as a first dose a quantity of the allergen which has never caused a local or general reaction in any patient. Starting from this first dose, he gives increasing quantities, injecting the patient for the most part every second day till the active dose is found.

INTERVAL BETWEEN TWO INJECTIONS

As long as very small doses of allergen are given, it is permissible to give daily injections, although as a rule we give them every second day. As soon as the *active* dose has been reached, we give injections twice a week, without further increasing the quantity injected.

A dose is considered to be active (*a*) *if the allergic symp-*

toms are favorably influenced. If all symptoms disappear, no increase in dose is necessary, nor is it advisable. It is unwise to attempt to obtain complete desensitization, as this will generally be impossible, and there is danger of making the patient more sensitive (see the instance of ipecac sensitization cited above).

(*b*) *If general reactions appear* (allergic attacks, collapse) the dose has been too great. The injections must be stopped for two or three weeks and the first dose of the new series should be one-thousandth of the one last given. It is always possible that, after too strong a dose, the patient has become to a greater or lesser degree desensitized. Indeed, some people advocate giving large doses on purpose, in the hope of obtaining rapid desensitization. This, however, should be considered as an inadvisable procedure, as it is dangerous, and may lead to a result the reverse of that expected (see case cited above).

DURATION OF TREATMENT

Even in those cases in which injections do not seem to ameliorate the patient's condition at first, the treatment should be continued until it has been definitely proved that no improvement can be obtained in this way. In all cases where definite signs of improvement appear, treatment should not be stopped until all symptoms have disappeared. This condition will sometimes be reached in two weeks, but sometimes injections will have to be made for a year or longer. In all cases where the injections have, at a certain period, given an unmistakable improvement, the treatment should be continued, changing the doses and the intervals without losing patience, till the desired result is obtained. Even if all symptoms have disappeared, in-

jections still should be given once a week, later once a fortnight and once a month for a period of half a year to a year.

The indications given hold only for cases which show symptoms throughout the year. In "periodical" cases (hay-fever) the same method can be applied, with slight variations, starting treatment before the beginning of the season, so that "the active dose" has been determined before the outbreak of attacks is to be expected. Some authors prefer to start treatment long before the beginning of the season, trying to immunize the patient before pollen occurs in the air. This method is less advisable, as (*v. sup.*) real immunization will never or almost never be obtained. Moreover, the method is dangerous, as it may easily happen that at the beginning of the season or later, such high doses are given that, together with the pollen present in the air, they constitute an overdose for the patient and produce an attack.

Consequently, if the immunization method is to be used at all, the doses injected should be reduced at the beginning of the season.

In periodical cases like hay-fever, usually it will not be sufficient to apply treatment during one season, but it will have to be repeated the next year. On this point we agree with the opinion of Cooke and van der Veer, and of Freeman, referred to previously. This means that treatment of hay-fever must be applied every year; this is another disadvantage of specific treatment.

The following is an instance of one of our very few cases of typical hypersensitiveness to *one* of the known allergens, in which specific treatment was very effective.

Boy, aged fifteen. Two brothers suffer from asthma.

This patient has suffered from severe attacks of asthma since early childhood. During the last few years he has always been very bad in the night between Saturday and Sunday and has to stay in bed afterwards for two or more days. The von Pirquet reaction is almost negative, all reactions with proteins are negative, and only dog's hair gives marked skin reactions.

Beginning of treatment:

26– 6–'21	1	c.c. of dog's hair	1/1,000,000	
30– 6–'21	5	c.c. of dog's hair	1/1,000,000	no attacks
3– 7–'21	0.5	c.c. of dog's hair	1/ 100,000	no attacks
6– 7–'21	1	c.c. of dog's hair	1/ 100,000	no attacks
9– 7–'21	1	c.c. of dog's hair	1/ 100,000	no attacks
13– 7–'21	1	c.c. of dog's hair	1/ 100,000	no attacks
16– 7–'21	1.5	c.c. of dog's hair	1/ 100,000	no attacks
23– 7–'21	1.5	c.c. of dog's hair	1/ 100,000	slight attacks
30– 7–'21	2.5	c.c. of dog's hair	1/ 100,000	no attacks
6– 8–'21	3	c.c. of dog's hair	1/ 100,000	no attacks
13– 8–'21	3	c.c. of dog's hair	1/ 100,000	no attacks
20– 8–'21	3	c.c. of dog's hair	1/ 100,000	no attacks
27– 8–'21	0.5	c.c. of dog's hair	1/ 10,000	no attacks
3– 9–'21	0.5	c.c. of dog's hair	1/ 10,000	no attacks
10– 9–'21	0.5	c.c. of dog's hair	1/ 10,000	slight attacks
17– 9–'21	0.5	c.c. of dog's hair	1/ 10,000	no attacks
24– 9–'21	1	c.c. of dog's hair	1/ 10,000	no attacks
2–10–'21	1	c.c. of dog's hair	1/ 10,000	no attacks
8–10–'21	1	c.c. of dog's hair	1/ 10,000	no attacks
22–10–'21	1	c.c. of dog's hair	1/ 10,000	no attacks
5–11–'21	1	c.c. of dog's hair	1/ 10,000	slight attacks
12–11–'21	1	c.c. of dog's hair	1/ 10,000	no attacks
26–11–'21	1	c.c. of dog's hair	1/ 10,000	no attacks
17–12–'21		no injection		no attacks
14– 1–'22		no injection		no attacks
11– 2–'22		no injection		no attacks
13– 5–'22		no injection		no attacks

This case shows that excellent results may sometimes be obtained with specific treatment, but it should be repeated that the result may be less good, and that the method may even fail altogether. In ten cases of very definite hypersensitiveness to an allergen mentioned in a previous section, viz., a substance contained in wheat infected with mites, we obtained only a (partial) desensitization with specific injections in a few cases, whereas the others were refractory.

From this state of affairs it results that often in cases with a known causative agent, non-specific treatment will have to be applied either alone or in addition to a specific treatment.

NON-SPECIFIC TREATMENT

Most authors agree that the exact mechanism of anti-allergic treatment is unknown; the ruling factor is the fact that injections of small amounts of an allergen reduce hypersensitiveness to that allergen. If therapy had to stop here, we should not be able to treat the vast number of allergic diseases in which the causative agent is unknown. This, however, is not the case. Experience has taught us that hypersensitiveness to a certain causative agent may be reduced also by the injection of small quantities of another allergen, provided that the patient is hypersensitive to this latter allergen too. Thus if a patient is hypersensitive to horse dandruff and nine other proteins, treatment with horse dandruff may be beneficial, irrespective of whether the horse dandruff has any connection with his allergic attacks or not.

In the author's view, in some cases where so-called specific treatment is applied, it is in reality a non-specific treatment.

It may be remembered that in so-called cases of bacterial sensitization, a treatment with autovaccine is often initiated. Cooke, in a recent survey of the literature of this point, acknowledges the beneficial effects this treatment may produce, but he denies a *specific* action in this case. Rackemann came to precisely the same result. I agree with Cooke and Rackemann, but I want to enlarge this view and extend it to some other cases of "specific protein treatment."

If in an allergic patient a number of positive intradermal skin reactions is found, not much time need be lost in trying to settle the question which protein has to be considered as the causative agent, but treatment can be started with one of the proteins.

We do not mean to say that it is entirely irrelevant which protein is chosen; some cases may react better to horse dandruff, others to dog's hair, still others to a certain autovaccine, etc.

Since all allergics react to an extract of human dandruff, treatment with such an extract would be rational in all these cases; the writer has applied it, but obtained doubtful results. However, long before the reaction to human dandruff was known to him, his attention had been drawn to another hypersensitiveness which is shown by nearly all allergics, viz., hypersensitiveness to tuberculin, and treatment with this "allergen" had been already started. In the beginning tuberculin was administered only in those cases in which no causative agent could be found, but the results of this treatment were so good that it was also used as an additional measure in cases in which specific (or so-called specific) treatment could be applied, but did not give a satisfactory result. During the last few years all our cases of allergy which showed hyper-

sensitiveness to tuberculin were treated with this substance. It must be remembered that hypersensitiveness to tuberculin is not always shown by a positive von Pirquet test, but may even in the absence of this be manifested by a rise in body temperature after its injection.

A connection between tuberculosis and asthma has often been supposed to exist and has as often been denied. We have been very much impressed by the high sensitiveness to tuberculin of many asthmatics and other allergics, although we have seen some cases which failed to react to the highest doses of tuberculin. We are convinced that, generally, asthmatics cannot be considered as sufferers from tuberculosis: on the other hand we tend to the view that in most cases a certain etiological relation between hypersensitiveness to tuberculin and allergy exists. It will be the task of work to be done in the future to investigate the nature of this relation.

Apart from these theoretical considerations, the fact that many allergics show great improvement of their symptoms after tuberculin treatment is undeniable. Many authors in Germany (Pondorff, Ranke,[73] and Liebermeister[74]), in Italy (Pietroforte[75]), in France (Bouveyron,[76] Bonnamour and Duquaire[77]), and in Belgium (Keersmaeker) agree on this point.

Isolated cases of tuberculin treatment in asthma can be found in the older literature.

Thus in 1897 Bussenius[78] communicated his experiences with tuberculin treatment on patients suffering from tuberculosis. The first patient of his series was a case of tuberculosis combined with asthma. After tuberculin treatment the attacks which had persisted during other treatment disappeared. Frankfurter[79] has published in

1913 seven cases of asthma treated with tuberculin; all the cases did well.

As a rule, however, tuberculin was, in these earlier cases, administered to sufferers from tuberculosis who showed symptoms of asthma at the same time. Regular tuberculin treatment, as a standard method of anti-allergic treatment with the definite object of obtaining a reduced hypersensitiveness in allergics, has been started only in recent years. Our first communication [80] on this subject was made in 1921. It is, however, only fair to state that the papers of Pietroforte and Ranke antedated our paper by one year. Bouveyron, who published his work only a few months after ours and quite independently, came to almost exactly the same conclusion.

TECHNIQUE OF TUBERCULIN TREATMENT OF ALLERGIC DISEASES

Before starting therapeutic tuberculin injections, it is advisable to apply a von Pirquet skin test with 100 per cent. tuberculin in order to get an approximate idea of the sensitiveness of the patient. It must be remembered, however, that a negative skin test does not prove that the patient is insensitive to tuberculin, nor does it exclude the possibility of efficient tuberculin treatment. Hypersensitiveness of the skin and general hypersensitiveness of the patient do not run parallel in the case of tuberculin, as in that of many other allergens. If the von Pirquet test is very intense, or if there is any indication that the patient might suffer from tuberculosis, we make the first therapeutical injection very small, using 1 c. c. of a dilution of 1/10,000,000. If the skin reaction is moderate and no danger of tuberculosis seems to exist, the first dose is 1/1,000,000, and if the von Pirquet test is negative or

nearly negative, the first dose may be taken as 1/100,000. After that we inject twice a week, making each dose 0.1 c. c. higher than the previous one. We continue in this way till

(*a*) all symptoms of allergy have disappeared, or

(*b*) a strong local reaction, or

(*c*) a general reaction appears.

In these cases the treatment is continued, but the dose is kept fixed at the quantity last given. Eventually it may be raised later.

Treatment must be continued for a considerable time, up to a year and sometimes longer. In the beginning injections are given twice a week, later once a week, and still later once a fortnight. Even in successful cases it may happen that after the injections have been stopped for about three weeks, allergic symptoms reappear. This is one of the points on which Bouveyron, who worked quite independently of us, obtained exactly the same results. In such a case tuberculin treatment has to be started again.

It sometimes happens that after an initial improvement the condition of the patient very gradually becomes worse again, whilst further injections do not seem to produce any effect. In such cases amelioration sometimes occurs suddenly if all injections are stopped. Obviously the doses had become too high in spite of all precautions.

All therapeutical tuberculin injections are given subcutaneously.

Pondorff applies tuberculin cutaneously, making a series of large skin scarifications first. We have in some cases followed this procedure, but obtained the impression that if subcutaneous injection fails, Pondorff's method fails also. Since it has, moreover, the disadvantage of not allowing of a careful estimation of the quantities effective,

and since we have found that Pondorff's claim that with his method no general reactions due to tuberculin are caused is erroneous, we have not felt justified in continuing with it.

If practised in the way described above, tuberculin treatment is absolutely harmless. However, two points should be kept in mind. The first is, that a negative skin reaction should not lead the physician to give too high therapeutical doses subcutaneously, since general reactions (allergic attacks, high temperature) may suddenly appear.

The second point is, that the rules given hold only for those cases in which no active tuberculosis is present. This possibility should be excluded by careful examination before treatment is started. In cases of asthma this examination may be considerably furthered by giving the patient a small dose of adrenalin subcutaneously, as this will often lead to the disappearance of râles and other signs in the lung, if due to the asthmatic condition only.

CHOICE OF TUBERCULIN PREPARATION

Up till now, we have always used Koch's T.O.A. This gives good results. Perhaps other tuberculins may have the same action; however, as long as this has not been proved, we advise the use of our preparation or of a similar one.

RESULTS OF TUBERCULIN TREATMENT

The majority of our allergic patients are sufferers from asthma, and consequently the results of our tuberculin treatment can be judged best in this illness. Up to now our statistics of tuberculin treatment include more than 300 cases of asthma, of which 15–20 per cent. remained absolutely uninfluenced. About fifty per cent. were completely or almost completely cured, while about 25–30 per cent. were distinctly or considerably improved.

In judging these results, it should be recognized that these figures include *all* cases of asthma which came under our care during the last three years, with the omission of only three patients who died some days after admission and before any antiallergic treatment could be started. On the other hand, it is only fair to admit that, although it has been definitely proved that bronchial asthma may be cured by the application of subcutaneous tuberculin injections alone, in many cases we had temporarily to take accessory measures also.

The effect of tuberculin treatment may show itself after the first few injections or it may be manifest only after some months. We always tell the cases this before starting, and lay great stress on inducing them to keep patient and not to discontinue treatment if they have to wait some months before improvement sets in.

Although we could not obtain improvement in all our patients, we are in a position to state clearly that our treatment never did any harm to any patient, with three exceptions. In two cases, during the earlier phases of our work, we gave too high a dose of tuberculin, with the result that it was followed by violent asthmatic attacks; after two weeks this condition passed off and improvement followed. Similar cases have previously been described in the literature long before tuberculin treatment was consciously applied to asthmatics.

In a third patient, tuberculin treatment was driven too far by a colleague who had misunderstood our instructions, and had continued to increase the dose of tuberculin after all asthmatic signs had completely disappeared. As a result of the application of the very high doses which he had reached in this way, the patient had fresh attacks of

asthma and had become hypersensitized to tuberculin to such a degree that asthmatic attacks ensued after the injection of doses of tuberculin 1000–10,000 times smaller than that which had been tolerated at the beginning. In this period we had to induce some asthmatic attacks before we found the limit of tolerance again. In all three cases the period during which the condition of the patient was worse by tuberculin injections did not last longer than a fortnight.

At the onset of our work on the tuberculin therapy of bronchial asthma we always had our patients admitted to a hospital before starting our injections. This was necessary since the mode of procedure was entirely new, effective doses had to be determined, etc., so that we did not feel justified in acting otherwise. Admitting the patients to the clinic, however, had one disadvantage, which became clearer to us as our work proceeded. The fact that in most of our asthmatics local influences play an important part as an etiological factor has been fully discussed in a preceding section of this book; as a consequence of these climatic factors in many of our patients, the attacks ceased without any treatment some days after entering the clinic. This made it difficult for us to estimate the exact therapeutic dose as long as they stayed with us. All we could do was to investigate whether they could stand tuberculin injections at all; if this point was settled, they were sent home and therapy was continued there. But since the active dose had not yet been reached, in many cases the attacks would reappear at home, and often only after a long series of injections would amelioration occur. We even noticed sometimes that the first attacks after coming home were more severe than before. The reason for this is now quite clear to us. These patients, mostly suffering

from asthma due to climatic influences, did not show attacks in the hospital, since allergens appear to be scarce there, but, during their residence with us, these patients lost a part of their resistance, so that there was an increase in the symptoms after returning home. As a result of these observations we have during the last year proceeded in an altogether different manner. We now take the patient into the hospital only if this cannot be avoided, but in nearly all cases the treatment is ambulatory from the onset. The patients come to our institute to be injected once a week, and later once a fortnight; sometimes we ask their family physician to give the injections, in quantities indicated by us, during the intervals. In this way all difficulties are met and our results are better than they formerly were.

It has already been stated above, that not all patients are influenced by tuberculin therapy; a certain number remains refractory, so that certain additional measures are necessary; also in those cases which do react, but not sufficiently, during the first period of tuberculin treatment, additional measures are wanted. These accessory measures will now be discussed.

ACCESSORY MEASURES

In all cases where severe attacks occur at short intervals, it is necessary to cut them down with adrenalin. We then proceed as described in a preceding section, permitting the patient to use adrenalin in quantities of 0.2–0.4 c. c. per injection. Usually as a maximum three or four such injections are allowed daily. We want to repeat that often in older patients suffering from asthma we obtained excellent results by telling them to take injections of 0.2 c. c. of adrenalin three times daily for many months,

irrespective of whether they considered these injections necessary or not. It may be added that this mode of procedure is also very useful in cases of bronchitis without asthma occurring in older people.

In addition to adrenalin injections, we often prescribe calcium chloride in large doses (ten grammes daily during ten days), and sometimes atropine in doses of from one to three milligrammes. Formerly we often gave benzyl benzoate by mouth and obtained the impression that it sometimes relieves the asthmatic attacks. Latterly, however, when benzyl benzoate was given, we nearly always prescribed its application by inhalation. The following prescriptions seemed to be useful:

℞

Benzyl benzoate	10 g.
Acacia	8 g.
Aq. ad	100 g.

Fiat emulsio pro inhalationem.

Inhalations with 5 c. c. four or five times daily.

Inhalations of the emulsion of benzyl benzoate may be useful and many patients appreciate them, but often they find that the emulsion irritates their mucous membranes and causes coughing; it has then to be given in a more diluted form.

If patients complain of coughing we often prescribe codeine, and we have found it useful to combine this drug with pot. iod. The following prescription is often given:

℞

Potass. iod.	15 g.
Codein hydrochlorid	1 g.
Aq. ad	300 g.

M. D. S. 3 d. d. 10 c.c.

All these measures may be of some help, but they will very seldom produce a lasting cure. This can be obtained only by one of the antiallergic methods. On the other hand, it has been proved that antiallergic treatment alone, without any additional measures, may effect a complete cure. We have treated as ambulatory cases a number of patients simply with injections of tuberculin without any additional measures. This makes us certain that tuberculin injection constitutes the main factor in the treatment of allergy; the other measures may be helpful but could be omitted if necessary. In fact, the number of prescriptions for similar drugs which we give our patients decreases steadily from year to year.

To illustrate the effect a tuberculin cure may have, we give two typical instances of very successful tuberculin treatment. It has already been mentioned that the doses of tuberculin to be injected vary very much from individual to individual and the real difficulty of this antiallergic therapy is to find the effective dose. It may be added in parenthesis that the result of this fact, which includes the absolute impossibility of giving rules for treatment which hold for all asthmatics, is that a physician who specializes in this treatment will be much more successful than the general practitioner. The latter, however, will also be able to obtain good results if he and his patients have enough patience. If dilutions of 1/10 million of tuberculin are injected in the beginning and the dose is raised as indicated above, it may be many months before the active dose is reached, and it may very well happen that during these months no improvement at all is noticed. This should not discourage the patient nor the physician; they should continue till the active dose is found. Only if injections of active doses give no result, may the method be considered

as useless in the case under observation. To this one other point has to added. If the dose is continually raised, it may be that the effective dose is gradually passed without the physician noticing it. It is difficult to explain such cases, but they sometimes occur. The only thing to do, then, is to go down to very low doses. These may give a local reaction and meanwhile ameliorate the patient's allergic condition. In one of the examples of treatment given below, such an instance occurs.

We deemed it necessary to give not only instances of successful cases, but also instances of those treated with little or no result. The latter will for the most part be found among those allergics who are so much influenced by climatic factors that any treatment fails as long as these factors cannot be eliminated.

This point will be discussed later on.

INSTANCES OF TUBERCULIN TREATMENT

A. Successful cases.

C. v. N. Girl, aged nineteen. Since childhood attacks of dyspnœa with bronchitis. The attacks lasted some weeks, sometimes for months. In the past years this condition has become more aggravated. Ringworm in childhood.

Treatment started September, 1922. Purin-free diet. Tuberculin injections as follows:

September	9	1922	T.O.A. 2/1,000,000	
September	23	1922	T.O.A. 4/1,000,000	
September	27	1922	T.O.A. 8/1,000,000	slight attack
September	30	1922	T.O.A. 1/1,000,000	

From October 4 until November 1, 1922, the dose was increased from 1/100,000 to 5/100,000, after the last dose the patient had rise of temperature, therefore the dose was

decreased to 1/100,000; after this the dose was slowly increased until December 13, 1922, when 1/10,000 was given; after that an injection was given once a week and after January 31, 1923, once a fortnight. From September 30, 1922, until January 31, 1923, the patient was continually well. Between January 31, 1923, and August 2, 1923, the dose was increased to 1/1000. In this period the patient had six attacks. From August 2, 1923, until October 8, 1923, doses were given varying from 1/10,000 to 1/1000, the patient had attacks regularly; therefore, on October 8, 1923, T.O.A. 1/100,000 was given and then the dose was increased very slowly, by injections twice a week. On November 2, 1923, 5/100,000 was given, and after that the dose was not altered. Since October 8, 1923, no further attacks. April 18, 1924, patient feels perfectly well.

In this case we see that a dose between 1/100,000 and 1/10,000 makes the condition better, larger doses make the condition worse.

L. v. d. V. Schoolboy, aged nine.

Asthmatic attacks since two and one-half years old, becoming more severe for the last three years. In winter an attack every month, which lasted some days. In summer an attack every two or three months.

His grandfather, grandmother, and three aunts from his father's side all had asthma. Treatment started 31–8–'21. At first he was treated with calcium chloride, three grammes daily. In the winter of 1921–1922 he had five attacks less severe and of shorter duration than formerly. In summer, 1922, he had occasional attacks. However, the treatment with calcium chloride was continued. In winter, 1922–1923, he felt worse than ever.

March, 1923, the treatment with tuberculin was started,

at first combined with small doses of milk, afterwards with T.O.A. only as follows:

March	26	1923	T.O.A.	2/1,000,000	
March	30	1923	T.O.A.	3/1,000,000	no attacks
April	4	1923	T.O.A.	4/1,000,000	no attacks
April	11	1923	T.O.A.	2/1,000,000	slight attack
April	18	1923	T.O.A.	3/1,000,000	no attacks
April	23	1923	T.O.A.	4/1,000,000	no attacks
May	2	1923	T.O.A.	5/1,000,000	no attacks
May	9	1923	T.O.A.	2/1,000,000	one attack

From May 9 until June 27, 1923, the dose was increased slowly up to 1/100,000. In this period the patient had an attack twice; after that the dose was increased rapidly. August 8, 1923, 1/10,000 was given and after this date injections were given once in a fortnight, and the dose was slowly increased until March 1, 1924, 1/1000 was given. This dose was continued once every three weeks. Since July 6, 1923, the patient has had no further attacks.

Conclusion: This boy with hereditary asthma has had more frequent and severe attacks every year. Regulation of the diet, and calcium chloride, gave temporary amelioration; afterwards the condition relapsed. Improvement, however, was evident following the administration of tuberculin injections in small doses. Later on larger doses were given and after that the attacks disappeared completely.

B. Case only partially successful.

No. 126. Wife of housekeeper, aged forty-seven years, with bronchial asthma since twenty-one years old. She has tried all sorts of drugs, including morphine. During the last few years her condition has been very bad. She has many attacks daily, and "burns" asthma drogues

very often. If she wants to go upstairs, she has to " burn " one before being able to do so. Tuberculin treatment was started with 0.5 c. c. of 1/100,000 and the dose gradually increased up to 0.5 c. c. of 1/10,000. She was also put on a purin-free diet, prescription JK, and codeine. After six months' treatment her condition was ameliorated. She often has one or two attacks daily but they can be cut down by administering 0.5 c. c. of adrenalin solution. Sometimes she is free from attacks for one or even two weeks. The patient is pleased with the result, and her life is much easier and more agreeable than it formerly was, but still no definite cure has been obtained.

C. Case treated without any success.

No. 121. A married woman with no children. No hereditary factors and no eczema in childhood. Asthma started seven years ago after bronchitis. Attacks of asthma, which were rare at the beginning, have become more frequent latterly. During the last year, the patient had six to eight attacks daily, for which adrenalin had to be given or asthma powder burned.

The patient was admitted to the hospital for treatment 29–9–'21. Tuberculin treatment with varying doses was given for one year. At the same time and afterwards, peptone and vaccine treatments (auto- and stock vaccine), milk therapy, and regulation of the diet have been tried, but the condition could not be changed at all.

This patient was injected for diagnostic purposes with an extract of house dust containing 0.00004 gramme of nitrogen. She entered into a *status asthmaticus,* during which adrenalin was of no avail at all, and which made us fear for her life during twenty-four hours. For a period

of two weeks her condition was worse than before; she then returned to her original condition.

It may be added that the injection which provoked this result gave a negative skin reaction; all other intracutaneous tests are negative in this patient, while also the von Pirquet reaction is almost negative.

SKEPTOPHYLACTIC THERAPY

Injections of milk, sulphur, and peptone treatment.

Since the efficient dose of tuberculin varies widely in different cases, and since too large doses may be dangerous, it will nearly always be necessary to start tuberculin treatment with an inefficient dose, which may gradually be raised to an active one. This implies that often some weeks will pass before this treatment can be expected to yield any result. During this time a direct improvement of the condition may often be obtained by applying skeptophylactic treatment, viz., milk, sulphur, or peptone therapy. This treatment must also be tried in cases which are not ameliorated by tuberculin treatment.

Milk injections, as a form of non-specific protein treatment, have been used in a great number of illnesses of varying origin. In some these injections are utterly useless, while in others they give valuable results. It seemed to us that this method should be tried in allergic cases on the basis of the following consideration. Notwithstanding all the differences in interpretation of the origin and treatment of asthma and allied diseases, there are some peculiarities in these illnesses which nobody denies. One of these is, that often during an acute infectious disease, a patient, who was suffering from severe allergic attacks before, will be completely free from all allergic symptoms, and this period of well-being may last up to three or four weeks

after the intermediary disease has been cured. Then the old condition of allergic attacks will reappear.

The disease which causes amelioration may be a bronchopneumonia (I know some asthmatics who feel most happy during periods of bronchopneumonia) or even influenza; it may also be tonsillitis or another acute illness. On the other hand, we know that diseases of the respiratory organs may also make the condition worse.

Knowing this, it is not very astonishing that injection of some material which provokes a " reaction," viz., a local aseptic inflammation and a general reaction, fever, headache, etc., may either ameliorate the allergic condition or make it worse. In the author's view, the possibilities and limitations of so-called skeptophylaxis are here disclosed. The injection of milk, sulphur, or peptone provokes a reaction, which may be good or bad for the patient. This will have to be tested out in any given case. I tend to the view that vaccine treatment, including autovaccine treatment, and also some instances of so-called specific anti-anaphylactic treatment, belong to the same group. Possibly the explanation of the result of tuberculin treatment will have to be found here too. Although the explanation of the fact that amelioration of the attacks during an illness or after injections of proteins is lacking, some light may be thrown on the matter by recent researches of Gottlieb and Freund. Some years ago the author and van der Made [81] demonstrated that under certain conditions intravenous injections of peptone may in animals increase the sensitiveness to adrenalin. Later Gottlieb and Freund [82] corroborated this fact, but they showed further that after intramuscular injections of milk or other proteins in rabbits, the sensitiveness of the animal to

adrenalin might remain increased for a period of some weeks (in our experiments the action of the peptone lasted only for some hours). Obviously this is one path which may lead to the explanation of the salutary action of protein injections in allergics, but, nevertheless, at the moment the problem may by no means be considered as solved. The statement that obviously the human body cannot endure two "reactions" at the same time, so that if one is induced artificially it cuts out the other one, does not explain the question, nor does it appear very scientific, but it is to the point, because it describes the facts as they doubtless occur.

MILK THERAPY

Our routine method in applying milk injections is as follows:

First day	0.1 c.c. of sterilized milk subcutaneously, followed six hours later by injection of 1 c.c.
Second day	2 c.c. subcutaneously
Third day	5 c.c. intramuscularly
Fourth day	10 c.c. intramuscularly
Fifth day	2 c.c. subcutaneously
Sixth day	2 c.c. subcutaneously
Seventh day	0.2 c.c. subcutaneously
Eighth day	0.1 c.c. subcutaneously
Ninth day	0.1 c.c. subcutaneously
Tenth day	0.1 c.c. subcutaneously
Eleventh and following days	0.1 c.c. subcutaneously

Generally the first and smaller doses are tolerated without any inconvenience, but after the larger injections of five or ten c. c. the patient will usually show general reactions consisting of headache, uneasiness, and rise of temperature, sometimes to forty degrees C. Simultaneously

with these reactions one of two things will occur. Either the allergic condition will be improved or in rare cases it may be impaired. If the latter possibility occurs, milk injections should be stopped or be continued with small doses only. If at the height of the general symptoms the asthmatic condition is considerably ameliorated, as often occurs to an astonishing degree, the injections are continued as indicated above. It need hardly be stated that according to the circumstances, changes must be made in the scheme.

In applying milk treatment in allergic cases the following points have to be kept in mind.

(*a*) It is always possible that the patient to be treated is hypersensitive to milk and accordingly the dose of ten c. c. ordinarily given at the onset of milk treatment in *non*-allergic cases might be fatal. Hence the preliminary injections of 0.1 c. c. and 1 c. c. must never be omitted.

(*b*) After a first series of milk injections has been given, the patient, although not hypersensitive before, may have become sensitized. Hence a second series of injections, to be given after an interval longer than eight days after the last injection of the first series, must again be preceded by a preliminary injection of 0.1 c. c. Disregard of this rule caused death in a case, and not even an allergic case, described by Lubliner.

A strong girl, suffering from gonorrhœa without any other illnesses, was treated with a series of intramuscular milk injections, which were very well tolerated. Eight days after the last injection of this series, she was injected anew. Some minutes after the injection she died, showing all the symptoms of anaphylactic shock. Other similar cases are known.

(*c*) If injections of five c. c. to ten c. c. of milk give relief of the asthmatic symptoms, further injections of smaller amounts will also often be beneficial. In these cases daily injections of 0.1 c. c. may be given for a period of two or three weeks. If after this time symptoms of asthma reappear, it may be necessary to increase the dose temporarily, but it may also be necessary to lower it to 0.01 c. c.

(*d*) Soon after the inauguration of milk therapy, commercial preparations containing milk proteins were put on the market and are now widely used. It is claimed that casein preparations, such as caseosan, give milder symptoms and should be of equal therapeutic value to milk. It has, however, been proved that milk after the removal of casein still exerts an action, so that it is certain that casein preparations are not identical with milk. Moreover, it is not at all sure that the general reactions produced by milk injections are noxious: perhaps they form an essential part of the treatment. As long as this point is not settled we prefer to use milk, which is obtainable always and everywhere, and is far less expensive than commercial preparations.

RESULTS OF MILK TREATMENT

One of the advantages of the milk treatment of allergic diseases is that the decision as to whether the therapy will be successful or not is reached in two or three days. If after the injection of five or ten c. c. the allergic symptoms do not diminish conspicuously, it is of no use to continue this therapy. In most cases milk injections will reduce the symptoms or abolish them. The improvement will last only for a period of from two days to three weeks. Hence,

it is necessary to continue the injections. But even after milk therapy has been applied for a considerable time the symptoms will tend to reappear if the treatment is discontinued. Therefore, we generally use milk therapy to tide the patient over a difficult period. Thus if a patient who is in good condition in a certain place has to go to another place where he will presumably have more attacks, we give him two large injections before he starts and have the treatment continued with small doses during the early period of his new residence. Furthermore, we often give milk injections during the first period of tuberculin therapy, in which the active dose of tuberculin has not yet been reached. As soon as the tuberculin injections begin to be effectual, milk injections are discarded. Sometimes milk injections tend to make the condition of the patient worse; this point will be considered later on.

The following case illustrates very well what may be hoped for from milk therapy:

Patient No. 181, aged forty-eight, by trade a greengrocer, with very severe asthma, hardly ever free from attacks, many attacks occurring each day. Being taken into the clinic, the von Pirquet test was found positive. Tuberculin treatment was given for six weeks, with the result that the patient feels much better, and the attacks are less frequent and less intense. Instead of being an individual who is continually uneasy, and an invalid, he has become a man who works the whole day through, although he has two or three attacks; between whiles he feels quite well. Thus tuberculin therapy was partially successful. The patient has an angina attack with a temperature of thirty-nine degrees C., and for two days has not a single asthmatic attack. When the former illness has passed off, milk therapy is tried as follows:

First day 0.1 c.c. of milk, 5 hours after 1 c.c. subcutaneously, temperature 37.3° C.
Second day 5 c.c. of milk, intramuscularly, temperature 39.1° C.
Third day 10 c.c. of milk, intramuscularly, temperature 38.5° C.
Fourth day 10 c.c. of milk, intramuscularly, temperature 38.7° C.
Fifth day no milk injection, temperature 37.4° C.

After the injection of five c. c., the attacks kept away, but returned after about two months, so that he was then in the same state as before the milk treatment; after continual tuberculin injections his condition improved still further.

PEPTONE INJECTIONS

Our indications for peptone injections are the same as those for milk injections. Most patients react better to milk, some to peptone; we have not yet found it possible to predict which will be the case, so that it has to be tested out in each patient. As a rule we use five per cent. solutions of Witte's peptone in physiological saline solution, the first dose being 0.1 c. c., which is increased till five c. c. have been reached. Small doses are given subcutaneously, large ones intramuscularly. Daily injections are given. Sometimes the allergic symptoms will increase definitely after peptone injections; the latter must then be stopped.

As far as I am aware Auld was the first to propose the use of peptone injections in the therapy of bronchial asthma. He gives intravenous and intramuscular injections, and claims to have had very good results. He prefers Armour's peptone to Witte's peptone, as the former is said to contain less toxic substances. Our results with peptone reactions are not so good as those of Auld, but

we did not give them a fair trial, since we used them only when tuberculin treatment was not successful. We incline to the opinion that in these cases peptone is equally worthless.

INJECTIONS OF SULPHUR

During the last year we have often given injections of sulphur instead of milk injections. Sulphur injections have the advantage that anaphylaxis is not to be feared; moreover, they give more regular reactions.

As a standard dose we have chosen one c. c. of a one per cent. suspension of sulphur in olive oil. This dose, if injected intramuscularly, will, in most patients, in about twelve hours produce a painful local reaction, with fever, headache, etc. This reaction will as a rule last for about twenty-four hours. If during this period the allergic symptoms diminish, it is advisable to continue with this therapy, but we then always try to find a dose which gives little or no fever and still improves the patient's condition. About 0.2 to 0.5 c. c. of the one per cent. solution will have to be given.

We have tried other preparations of sulphur, among them a completely clear colloidal solution, but we definitely obtained the impression that the simple suspension is the better.

This therapy sometimes gives remarkable results, and sometimes it is worthless. In four cases of asthma combined with eczema of the face and body which had defied all other forms of therapy, we obtained an astonishing amelioration of the eczema in a remarkably short time. It has to be added that the dose of one c. c. of the one per cent. suspension may increase the allergic symptoms,

as we noticed in one case. Smaller doses, however, later, gave excellent results in that case.

It sometimes happens that weekly injections of ca 0.5 c. c. of sulphur improve the condition but that after some months the patient gets worse again. In such a case the dose of sulphur has to be reduced considerably. As a rule we then give 0.1 c. c. of a one pro mille suspension.

Formerly we sometimes used injections of sodium nucleinate; they may also give good results.

THERAPY WITH EXTRACT OF HUMAN DANDRUFF

Since nearly all allergics react positively to the injection of an extract of human dandruff, it may be anticipated that treatment with these extracts will prove successful. We have made some attempts in this direction, but our experience does not as yet permit us to draw definite conclusions.

PEPTONE TREATMENT PER OS

French authors have shown that in a number of cases of allergic disease, where alimentary factors are responsible for the onset of the allergic attacks, amelioration and even cessation of the attacks may be obtained by inducing the patient to take half a gramme of peptone three-quarters of an hour before every meal. This treatment sometimes gives remarkable results, but often it fails absolutely. As it is harmless, it should be tried in every case in which alimentary factors are supposed to play a part. It must, however, be remarked that we have seen two cases in which half a gramme of peptone (Witte's peptone in one case, and Armour's peptone in the other) produced an asthmatic attack after half an hour. The peptone must be taken exactly three-quarters of an hour before every meal. No food whatever should be taken between meals. If the

treatment is successful, it will be apparent after some days. It must then be continued for one or two months and may then be gradually stopped. If amelioration of the symptoms is not reached after the first few days, further oral administration of peptone is useless.

CASES OF ASTHMA UNFAVORABLY INFLUENCED BY MILK INJECTIONS

As has been related above, milk injections will sometimes increase allergic symptoms. These patients must usually be considered as hypersensitive to milk; the majority also will not tolerate milk when given *per os*. In none of our cases was the patient himself aware of this fact.

It goes without saying that milk, butter, and cheese have to be omitted from their diet. Sometimes it is possible to make use of this hypersensitiveness to milk by giving them injections of very small quantities of milk (0.01 c. c.). This may improve their condition.

DIET IN ALLERGIC DISEASES

In all cases of allergic disease a search has to be made for a possible specific dietary factor. Real cases of so-called "*anaphylaxie alimentaire*" certainly exist, but they are very rare. Still, in most instances dietary factors play a part in the allergic disease. Since we found (*v. sup.*) that practically all asthmatics show a disordered purin metabolism, we have made it a rule to prescribe for our allergic patients a purin-free diet (meat, fish, and leguminosæ are to be omitted). In most cases we gathered the impression that this diet was beneficial, and continued it for at least one year. In some cases, however, quite a different diet has to be given. We found that a number of patients do not stand dairy products, so that these have to be omitted; sometimes also eggs are poorly

tolerated. In these cases it will of course be necessary to allow meat and fish, as otherwise it would be impossible to get the necessary amount of protein food.

Apart from the facts that food rich in purins has to be discarded by all allergics, that a certain group does not tolerate dairy products, and that in some rare instances one specific foodstuff is the sole agent of the allergic attacks, there has to be considered a group of asthmatics who are suffering from what has been called by us the nutritive form of bronchial asthma.

NUTRITIVE FORM OF BRONCHIAL ASTHMA

In these cases alimentary factors play an important part in the causation of the attacks, only it is not one foodstuff or one group of foodstuffs which is noxious, but nearly all foodstuffs may give rise to attacks in a greater or lesser degree.

Varekamp and the present author have described a number of these cases as a nutritive form of bronchial asthma. In our experience this group includes about ten per cent. of all asthmatics, although food factors may play a less dominant part in many other cases of bronchial asthma and other allergic diseases.

Patients suffering from the nutritive form of bronchial asthma mostly show continuous slight symptoms of asthma, with more or less frequent exacerbations into severe attacks.

If all food is withdrawn in these patients for twenty-four hours, a slight amelioration of the condition may be obtained. But withdrawal of all food for another twenty-four hours will cause a complete or almost complete disappearance of the asthmatic symptoms. Any food which is given afterwards will tend to produce symptoms again,

but luckily some foodstuffs are less noxious than others. Usually a simple diet of cooked rice and tea is best tolerated. The food should be given in small portions and at frequent intervals. After a few days some additions to this simple diet are necessary. Each new foodstuff should be carefully chosen and its influence on the patient's condition carefully studied. Many patients tolerate milk, butter, vegetables, and bread, while others will have to live on meat, fish, eggs, and vegetables only. A small number of patients will be easily cured in this way; usually, however, after food has been given for one or more days, symptoms of asthma will reappear. It is then necessary to insert one or two fasting days and after that to start afresh.

Further details cannot be discussed here. It may only be mentioned that in nearly all cases we succeeded in finding the appropriate diet. On the other hand, we failed to do so in some cases, although we had occasion to study them thoroughly.

Relative to dietary factors, one last remark has to be made. It must be understood that tolerance and nontolerance of a certain foodstuff are by no means fixed entities. A foodstuff may be well tolerated one day and produce violent attacks another day. In a preceding section we have discussed the influence of climatic factors. It is worth noting that such factors may also influence the dietary component. We have seen cases who tolerated rice quite well in one place, but not in another at fifty miles' distance.

THERAPY OF ALLERGIC DISEASES IN RELATION TO CLIMATE

We have in the course of our discussions repeatedly called attention to the fact that in many instances a sufferer from allergic disease will be completely free from

attacks as soon as he goes to a place with a different climate or even if he enters a hospital. This not only holds for cases of Dutch origin but also for the majority of cases in England, north Germany, and America, and the English and Dutch colonies. Probably in many other countries the same phenomenon exists, but the author has no special experience of it.

It is almost certain that any patient who shows this peculiarity, viz., freedom from attacks in a hospital, will also be quite normal and without any sign of allergic attacks as soon as he is taken to places higher than 1500 to 1800 m. above the level of the sea. If this is true, the question arises as to how far this fact may be utilized for the therapy of allergic conditions. Relative to this it may at once be stated that a therapy which consists of sending a patient for some months to the mountains will as a rule bring only disappointment. Certainly the patient will feel very happy and will feel like a normal man up in the mountains, but after returning home, he will in a very short time be in exactly the same state as he was before going away. In many cases the improvement will not even last till the patient has reached his home, but he may begin his attacks on the way back. Nor is it certain that the patient will return to the state he was in before leaving; we often noticed that during the first weeks after coming home, the condition was even worse than before. All this is quite intelligible. As soon as the allergic patient arrives at a place where the air is free from those allergens which are noxious to him, he will be free from attacks, but he will by no means be cured so as to have lost his hypersensibility. This hypersensibility, this allergic state, remains unchanged during many months and even many years, although during all

that time no attack may have occurred. The author has seen numerous instances in which hypersensitiveness in such cases appeared to be in no way reduced even after six or ten years. On the contrary, a complete absence of allergens may even cause a temporarily increased hypersensitiveness, as a certain degree of resistance present may, owing to the absence of any reaction, become lost.

A short residence in a mountain climate, then, will as a rule bring about no change in the patient's condition; it will give him only a temporary respite. If a patient is financially and also in other ways independent, there is nothing against his taking a respite from attacks, or even many respites, every year. If, however, no such independence exists, and if a temporary residence in a mountain climate can be achieved only with great difficulty and heavy financial sacrifices, the author very decidedly dissuades the patient from this step. In such cases everything should be done to treat the patient at home and (as has been discussed above) during treatment taking the patient even temporarily into a hospital should be avoided. Only in very severe cases, where death is menacing, must one sometimes deviate from this rule; such cases may have to be admitted to a hospital or sent to the mountains.

The question, however, wears quite a different aspect, if it is possible for the patient to change his residence permanently. For many people this is impossible, but on the other hand there are a certain number of allergics who might quite well be helped by a change of residence if only they knew to what place they should go. A physician who has treated a number of cases of allergy will easily be able to give general indications about places which as a rule are " bad," and about others which as a rule are " good "

for allergics. In every case, however, the patient himself will have to test whether a certain place is really convenient for him. Before taking measures for establishing himself permanently in a certain town, the allergic should temporarily, for some weeks at least, stay in that place, and as close as possible to the house in which he will probably have to live afterwards, in order to test whether he is indeed free from attacks there or not.

One important point relative to the choice of a permanent dwelling-place should be mentioned. The patient must choose a place which is just at the limit at which he is able to live in comfort. If, for example, a patient knows that he is quite free from attacks at a level of about 500 m., it would be very unwise to choose, as permanent or temporary residence, a place at 1800 m., for the following reason.

Allergic substances are never completely absent from the air; there are more of these substances at lower levels and less in the mountains, but they are never completely absent. Now we have seen that a complete lack of allergen in the air may lead to a loss of resistance in the patient. His sole chance of being more or less desensitized consists of coming into frequent contact with subliminal doses of the allergen. Hence, it will be useful for him to choose a place not much above the level of his tolerance; this will enable him to inhale his allergen daily in small subliminal amounts, and may tend to increase his resistance.

Has a permanent residence in the mountains to be really permanent? In many instances this certainly is the case. I have seen people who had lived in some asthma-free place in California for ten years and more, and who got attacks almost the same day that they arrived

in Holland. We have observed the same thing in children who have been educated at schools in the mountains of Switzerland.

On the other hand, it must be admitted that, especially with children, the possibility exists that after a residence of some years in the mountains, the allergic condition may have passed away. However, when children or adults are sent from home to other climates in order to avoid allergic attacks, all calculations and plans should be made on the supposition that the change will have to be permanent. If, later on, it can be shown that the allergic state has indeed passed away, this should be considered as a fortunate chance which was not to be anticipated.

We have in the preceding section always spoken of mountain climate; it goes without saying, however, that a climate which is salutary for an asthmatic need not always be a mountain climate. Sometimes a sea—or any other climate in which allergens happen to be scarce—will do just as well. Even in Holland, where there are no mountains at all, change of residence within the limits of the country will often suffice. Only in very severe cases will mountain climate be indispensable.

It might almost be superfluous to state that the term " allergens " used in this connection is not a fixed entity. Substances which may be allergic for an allergic born in Holland need not be allergic for an allergic born in America. Still, it is remarkable that asthmatics from very different countries often agree fairly well as to the places all over the world which have to be considered as " bad " or " good." And if climatic factors play any part at all in the case of a certain allergic, it may be predicted with almost absolute certainty, that mountain air at about 1500 m. will do him great benefit.

MOUNTAIN CLIMATE COMBINED WITH ANTIALLERGIC TREATMENT

The statement that change of climate of short duration does not materially improve the patient's condition need not hold if the patient is treated antiallergically during his residence in a mountain climate. This is a point which needs to be emphasized. Physicians in mountain sanatoria should make themselves acquainted with the technique of antiallergic treatment; if they could give proper treatment, there would be a chance of really benefiting the patients.

In a certain respect these physicians are in a difficult position, since their patients do not show symptoms in their sanatoria, and consequently it is very difficult for them to judge whether antiallergic treatment has gone far enough. In other respects, however, the physician in a mountain sanatorium is in a very agreeable position. For those who apply the antiallergic treatment at home there is always the possibility of injecting too much allergen, since they do not know how much of the allergen will at a certain moment occur in the air. In the mountains this quantity is negligible, so that the physician there has much less risk to run.

THE MIASM-FREE CHAMBER *

For many patients it is impossible to change their dwelling-place even temporarily. A great number of them may be helped by tuberculin therapy or some other forms of antiallergic treatment. However, it is a known fact that a considerable number of severe cases cannot yet be helped by any of the known therapeutic measures. If they belong to the " climate " type a permanent residence

* Our first paper on " The Miasm-free Chamber " appeared in Proc. of the Royal Soc. of Med., London, April, 1924, Vol. xvii, p. 19.

in the mountains would save them, but, as has been said, very often this is impossible, since many people are able to earn their living only in certain places. Under these conditions the patient may still be helped in a way which has recently been tried by us and has been shown to be effective.

On the basis of our conception that asthmatics of the " climate " type, i.e., asthmatics subject to local influences, are allergics, hypersensitive to an unknown group of allergens occurring in the air, we have postulated that these allergics will be free from attacks whenever they are in a room which is hermetically closed, but ventilated continuously with air filtered so as to be free of miasms. Such a chamber has indeed been constructed by us and it has been placed in a room of the house of one of our most severe asthmatic patients in Rotterdam. If this patient, a girl of twelve years, enters her parents' house, she gets an asthmatic attack after three hours, and subsequently she will have an attack every two or three hours; these attacks disappear after adrenalin injection, but the adrenalin has to be given once every two or three hours. This condition lasts for two or three days; she then enters into an asthmatic state, and is permanently dyspnœic, while adrenalin is no longer effective. After two or three more days, a bronchopneumonia sets in with high fever, and if the child is not at once transported to a clinic in another place, she would certainly die. This has been confirmed three times during the last year. In the chamber constructed by us and placed in this same house, the child has been able to stay for five months, in the same condition that prevails during her stay in a hospital at Leiden. Furthermore, it was noticed that in three instances in which, without the child's knowledge, the filtration of the air was defective, she at once got more attacks. One day the motor which

worked the ventilation of the room was defective; twenty-four hours later the child had attacks every two hours. After the repair of the motor, she returned to her original condition again in three days.

Lately the experiment has been repeated with ten other patients with thoroughly good results.

We have shown, then, that in principle the miasm-free chamber may be effective. We are now attempting to convert the principle into a form which may be useful in practice.†

One remark may be added. If the system of a miasm-free room is adopted for a patient, this need not imply that he must always stay in that room day and night. There are some people who do not tolerate the air in a certain place for more than an hour. These people will, in such places, be continually in an asthmatic state and consequently in bed. For these people, then, to have to stay permanently in a room *without* attacks would always be the lesser of two evils. But many other allergics are able to tolerate the inhalation of miasms for half a day or even a day. These might be helped by staying in a miasm-free chamber during the night only, eventually also during part of the day. Since the miasm-free chamber may be made as large as is wanted and may offer every comfort any other room gives, there would be nothing against the system from this point of view. The only real obstacle will be the financial side of the question. The price of the chamber has to be such that the majority of people will be able to buy it; this point has not yet been completely solved. Apart from this, however, the author is in a position to state,

† During the last months we have succeeded in working out this problem satisfactorily, so that the miasm-proof chamber is now used by a considerable number of patients in our clinic as well as in their own houses, with remarkably good results.

that in principle it is possible, by making use of the miasm-free chamber, to relieve allergics who belong to the " climate " type. And it may be repeated that the " climate " type of asthma includes more than eighty per cent. of asthmatics in my country, and apparently a percentage not much lower in England, north Germany, America, and the colonies.

* * *

In the above pages the author has tried to give a general survey of diagnosis and treatment of allergic disease. For convenience' sake the survey is followed by a short description of the routine methods used by us in the different forms of allergy.

THERAPY OF BRONCHIAL ASTHMA

In rare cases a careful interrogation of the patient will reveal the cause of his attacks; if this happens, one must try to verify the communications of the patient by making him respire air which contains the antigen, or by giving him the latter by mouth if a foodstuff is concerned.

If interrogation does not reveal the causative agent, one has to try to find the cause by means of cutaneous reactions, but they will be successful only in a minority of cases. Then intradermal tests may be made, but, as has been fully discussed, they usually show only that the patient is hypersensitive to *some* allergen, without giving an opportunity of identifying the real cause or causes.

The same result may be obtained by the intracutaneous injection of the extract of human dandruff.

All the extracts used may be simple watery extracts of the material to be tested. Formerly, we first treated the material with ether and then extracted with a slightly alkaline solution, but we now know that the substances which act as allergens are easily soluble in ordinary tap-water. Many of them stand heating to 100 degrees or even 120 degrees C. The extracts have to be filtered through a Berkefeld filter to ensure sterility. Proper dilutions are made with a physiological saline solution containing one-half per cent. of phenol. All extracts are prepared in our own institute.

If the cause of the attacks is found in the way described, the first thing to do is to ascertain whether it is possible for the patient to avoid contact with this substance. If a foodstuff is concerned, this can usually be omitted from the menu, but if the substance is active on inhalation, avoid-

ance of contact with it may be more difficult. If it is uncertain whether the substance can be avoided, or if it is impossible to do so, treatment must be undertaken. Therefore intracutaneous skin tests with various dilutions of the extract have to be made. As a first therapeutic dose, for the most part 0.1 c. c. of the lowest concentration of the extract which barely gives a positive skin test may be given. This extract is then injected every second day or twice a week, in increasing doses. We usually give 0.3 c. c. as a second injection and 1 c. c. as a third. Then we give 0.3 c. c. of the next dilution, after that 0.5 c. c. or 1 c. c. of that dilution, and so on, as indicated in the general rules laid down in a previous section. As has been related above, we prefer, for the most part, to inject as a first therapeutic dose, a quantity so little that it never produces untoward results in asthmatics; starting from this quantity we gradually increase the dose as described.

If the causative agent cannot be found, and skin reactions (for example, with extract of human dandruff) indicate that it is, nevertheless, a case of hypersensitiveness, the first thing to do is to ascertain whether climatic factors may play a part. If this is so, as usually will be the case, this point must be explained to the patient, and it has to be made clear to him that if it is possible for him to change his dwelling-place he may perhaps be free from attacks during the rest of his life. In some cases a change within the country may suffice. However, in severer cases, a greater change will be necessary. Of course strict indications of suitable climate, which hold good for every patient, cannot be given, but generally speaking, it may be said that in proportion as a place has a higher altitude it is the more likely to be beneficial for an asthmatic. It may be repeated here, that, for the reasons stated above,

it is wiser to choose a place at the minimum altitude at which the patient is just free from attacks. He thus has the best chance of being desensitized. If the patient desires to be able to return to his home later, he will have to be treated at his mountain residence.

In the numerous cases in which a permanent change of dwelling-place is impossible, treatment will have to be started. This also has to be done when a change of dwelling-place, though beneficial, has not had a sufficiently good result. Of the several forms of non-specific treatment which have come under consideration, we always choose tuberculin treatment to begin with. Frequently during the last few years we have, subsequently to publications on the use of other methods, applied other substances, vaccines, peptone, etc., but we always had to return to tuberculin treatment. Of course, we by no means wish to presume that it is an ideal treatment, we only find that it is often helpful and is for most cases the best treatment at our disposal. The rules for applying tuberculin treatment have already been given. With regard to a recent publication by Cheinisse,[83] in which our method is criticised, we wish to make some additional statements. Cheinisse doubts whether tuberculin treatment is effective for two reasons:

(1) We put all patients to bed for two or three weeks, and it is known that taking a patient into a clinic often stops the attacks.

(2) We did not apply tuberculin treatment alone, but also gave adrenalin injections, prescribed codeine and potassium iodide, and regulated the diet, etc.

It cannot be denied that there is some truth in this criticism, although we have already pointed out in our first publication [84] on the subject, that according to our experience these accessory measures alone will never bring

about a cure which lasts after these measures are withdrawn, so that it is only the tuberculin which makes the therapy really efficient.

Moreover, we have in later years changed our method, so that Cheinisse's criticism is no longer applicable. First, we never now take the patient into a hospital for treatment, if it can be avoided. In this way our results during the first weeks of treatment seem to be less good than they formerly were, especially since we have lowered the first dose to be given. But after some weeks our results are even better now than before. Besides, we have now given ambulatory treatment to a number of patients, without giving them adrenalin, codeine, or any other drug, and the results have often been very good. Although we still hold the view that in a certain number of cases additional measures are indispensable, there is no doubt now that tuberculin injections constitute the really efficient part of our therapy.

As has been said, tuberculin is not an ideal drug, and a number of cases remain unchanged or insufficiently improved. In these patients we try to obtain amelioration by the injection of milk or sulphur. This will often give an additional improvement, and if so, it has to be continued for a considerable time, as indicated above. Usually milk and sulphur will act best in those cases which also yield more or less to tuberculin treatment, but we have also seen patients whose condition could not be changed at all by tuberculin, and who yet showed a great improvement after injections of sulphur or milk.

If tuberculin, milk, and sulphur are without effect, it is almost certain that the patient is extremely sensitive to climatic factors, and consequently all other measures taken, vaccine, autovaccine, or peptone therapy, etc., will then be

useless. If miasmatic factors are very potent, no therapy will be of help, and the only thing which can be done, if temporary improvement is desirable, is to send the patient into a hospital in a place where miasms are not present in large amounts or to send him to the mountains. As far as our experience goes, every asthmatic (perhaps with the exception of five or ten per cent.) may be temporarily improved in some weeks if he is taken into a hospital or sent to a mountain climate. This demonstrates the enormous influence of climatic factors. If a well-conducted therapy of bronchial asthma fails, this is nearly always due to a too strong influence of miasms.*

Diet. As a rule we prescribe for all sufferers from asthma a purin-free diet; if, however, after some weeks, no improvement is to be recorded, we often change it and give a diet entirely free from dairy products. If this does not improve the condition materially we return to the purin-free diet.

As has been stated above, at the very beginning of treatment, the patient is questioned as to the possibility of specific foodstuffs being noxious for him; in doubtful cases, cutaneous skin reactions may be helpful. It has also been mentioned that in the larger number of cases no specific food factors are found. Even then it may be possible that nutritive influences should come under consideration. There is a very simple way of finding out whether, during the whole course of treatment, attention has to be paid to nutritive influences or not, viz., the patient is asked to fast for forty-eight hours (twenty-four hours are not sufficient). If after that time the symptoms are not decidedly improved, little need be expected from dietary therapy. If, however, the patient's condition is much

* *Vide* footnote on miasm-free chamber, p. 115.

ameliorated during the fast, the occurrence of food factors is probable, and the main thing to accomplish is to find out whether a specific factor prevails or whether the patient belongs to the nutritive form of bronchial asthma described in a former section. The therapy and regulation of diet in cases in which food factors prevail have already been discussed.

THERAPY OF HAY-FEVER

The therapy of hay-fever is much simpler than the therapy of asthma, and this is even more true of its diagnosis. Blackley, who first understood the real cause of hay-fever and was thereby the founder of the modern theory of allergic diseases, already knew that in hay-fever patients, not only are the mucous membranes of the conjunctiva and nose hypersensitive to pollen, but also the skin shows a strong reaction if pollen is applied to a scarification. As far as I know, there is no exception to the rule that every sufferer from hay-fever will show positive *cutaneous* tests with the same pollen that causes his attacks, although the intensities of the reactions of mucous membranes and skin do not run parallel. We tend to the view that the reaction of the conjunctiva is more specific than that of the skin.

In early cases of hay-fever, i.e., cases showing symptoms only during the first months of the summer (from May till July, differing a little from country to country and from year to year), grass-pollen and the pollen of rye are usually the causative agents. Of the different grasses, timothy is the most important. Whoever possesses samples of timothy and rye-pollen will be able to diagnose and treat many cases of early hay-fever.

Pollen and pollen extracts may be bought from some firms which specialize in this matter. We prefer always

to have a stock of dry pollen of different species gathered by ourselves and make the extracts and the various dilutions as required. Timothy and rye may be bought, as has been mentioned, but in addition to these, a physician who expects to have to treat many hay-fever patients should keep a small stock of the pollens of various other grasses also. It is not difficult to collect pollens. During the time of flowering a sufficient number of plants are picked, which are then put into cylinders standing on a large sheet of filter paper. Every day all the plants are touched and shaken a little so that the pollen falls down onto the paper. This pollen is then gathered, dried, and stored in small bottles, in which it may be kept for two or more years.

In the late cases of hay-fever (showing symptoms up to September or even October), or in the mixed cases, special attention has to be directed to several flowers, viz., chrysanthemum, dahlia, zenia. clematis, spartina, aster, etc. The species concerned will vary from place to place. A specialist in the treatment of allergic diseases will need a stock of the pollens of the most important flowers which are prevalent in his vicinity.

Some people evade the difficulty by using for diagnosis and treatment a so-called polyvalent extract of pollen, containing the extract of a large number of pollens. The author feels that this method is wrong. Many patients may be sensitive to various pollens, and the degree of sensitivity to each pollen will differ. Hence, a dose which contains enough of one pollen may contain a hundred times too much or too little of another. Therefore, in my opinion, the rule must be observed that, if pollen treatment is applied at all, it must be done with a separate extract for each pollen.

The easiest way of making a correct diagnosis in a case

of hay-fever is to make a number of skin scarifications on the forearm of the patient and put a very small quantity of pollen on each scarification, together with a drop of water or of 0.1 N.NaOH solution. If the patient is sensitive to one or more of the pollens, he will show a large white wheal surrounded by a wider zone of redness; often he will complain of itching at the site of the wheal. In this way a specific diagnosis can easily be made in half an hour. Only in the rare cases of hypersensitiveness to a very uncommon plant may difficulties arise.

If the specific factor is found, specific treatment may be applied. Many authors advise starting treatment early in the year, for example, during the first half of February. They give injections with high dilutions in the beginning and increase the dose every time, trying to reach as high a dose as possible, so as to get a complete desensitization or an immunization. Possibly this method may give good results, but there is no doubt that it often fails. Large doses may even make the patient's condition worse.

Since the author noticed that in some cases in which specific treatment applied by others in the way described had failed, while tuberculin treatment brought amelioration, he has adopted the following procedure for the treatment of hay-fever. About February a specific diagnosis is made and the skin sensitiveness is quantitatively determined by intracutaneous injections of our stock extract of this specific pollen. Then no further pollen injections are given but tuberculin treatment is started. At first small doses are given (about 1/1,000,000), but they are increased (*v. sup.*) till a local skin reaction is observed; then the dose is no more increased, though later it has eventually to be changed, but weekly injections with it are given all through the season. In severe cases of hay-

fever this procedure may not be sufficient to keep down the attacks; injections of low doses of pollen extract are then given. The first dose to be injected is 0.1 c. c. of the lowest dilution that just gave a positive skin reaction, and this dose is gradually increased till the desired result (cessation of the attacks) is attained. This dose may be injected, if necessary, every second day, but in most cases it will have to be used only occasionally.

The next year the same procedure is followed, but the number of pollen injections will be much less than in the preceding year, and in the third year the condition will be still better. Our experience with the combined method goes only as far back as three years. Yet we are convinced of its effectiveness, since we treated with good results a number of patients who had not done well before with pollen treatment only. As it is sure that pollen treatment alone may be effective, and as we have found that sometimes tuberculin treatment alone may also be beneficial, and since in our combined series *all* patients have been benefited and some have been completely freed from attacks (nearly all these cases were very severe ones which had tried every other method before), we feel justified in advocating this combined method and in preferring it to the simple method described above.

Sometimes a patient consults us for the first time during the hay-fever season. The best course to follow then is to test out his sensitiveness to pollen and to start both tuberculin and pollen therapy at the same time, using small doses.

It goes without saying that, as in all other cases of tuberculin treatment, here also a complete examination of the patient must precede it, so as to exclude the possibility of the existence of tuberculosis, which would of course

change the indications and dosage of the tuberculin treatment.

OTHER THERAPEUTIC MEASURES

Dunbar and his co-workers, after a study of the relation between pollen and hay-fever, have tried to immunize animals with pollen. They succeeded first with the smaller laboratory animals and later also with horses. The serum of horses immunized with various kinds of pollen and so-called polyvalent sera have been put on the market under the name of *pollantin.* We have shown earlier in this book that pollen is a very poor antigen. In fact Dunbar and his collaborators do not obtain immune reactions with their immune sera. They believe, however, that they can demonstrate the existence of specific antibodies in their sera in another way. They first determine the minimum quantity of a certain pollen extract which causes a distinct reddening if brought into contact with the conjunctiva of the eye of a sufferer from hay-fever. They then find how much serum has to be added to prevent this action. Obviously, accurate determinations may be made in this way. Prausnitz,[85] says that the error of this determination need not exceed ten per cent.

The conception of Dunbar and Prausnitz is not generally accepted. That their pollantin may inhibit the action of pollen is beyond doubt, but Weichardt states that normal ox serum has the same action, so that it would not be necessary to ascribe antigenic properties to pollen.

The therapeutic application of pollantin has been tried in two ways, viz., subcutaneous injection and local application. The first method does not seem to have given encouraging results, as the pollantin appears to be toxic. If small doses are given, this toxic action is less distinct, and attacks do really seem to be reduced after this applica-

tion. Injections, however, have to be repeated every second day. Generally, local application is preferred. Pollantin may be used as such, or dry, as a powder, or in ointment. The substance has to be applied to the conjunctiva before symptoms of hay-fever appear. Treatment has to be repeated every day or several times daily; moreover, the patients must try to avoid the presence of pollen as much as possible, but if they follow up all indications carefully, fifty to sixty per cent. may obtain good results. The statistics of the " Heufieberbund of Helgoland " differ somewhat from Prausnitz's figures. The " Bund " registers complete success in from one-fifth to one-third of cases and partial success in one-fourth. In those cases which were not favorably influenced, damage may even be done. Prausnitz assumes that the patient has then become anaphylactic to horse serum, so that the application of normal horse serum also produces symptoms of conjunctivitis. These people could be helped by the use of an antiserum from rabbits.

Besides pollantin, another hay-fever serum exists, viz., graminol.

Graminol is the serum of cattle taken during flowering season. It is freed from salt by dialysis and afterwards dried, and the method of application is the same as for pollantin. According to the " Heufieberbund " graminol is better than pollantin, but others hold that the reverse is true.

The preparation of graminol is based on Wolff-Eisner's theory of hay-fever. He holds that in the blood of normal individuals cytolysins occur which are able to disintegrate pollen, so that irritating substances are formed. Normal blood, however, also contains antilysins, which are absent from the blood of hay-fever patients. The blood of cattle

during the flowering season is supposed to contain great quantities of antilysin, hence the use of dried blood in hay-fever.

The author has had no personal experience of treatment with pollantin and graminol.

Before finishing a discussion on the treatment of hay-fever the various procedures which serve to relieve acute attacks should be mentioned. A large number of powders and fluids for vaporization are on the market, for the most part containing adrenalin, cocaine, asthmolysin, or atropine. Some people prefer one, others another preparation. Most of these remedies give temporary relief.

The claim that asthmolysin, which contains beside adrenalin a small amount of hypophysin, would act better than adrenalin has, as far as the author is aware, never been experimentally proved.

Finally, one has to be reminded that the subcutaneous injection of adrenalin will give temporary relief to all kinds of allergic attacks and consequently to hay-fever also. In very severe cases subcutaneous application of this drug can hardly be omitted, the dosage and method being as described under asthma.

THERAPY OF VASOMOTOR RHINITIS NOT DUE TO POLLEN

A certain number of patients suffer from symptoms similar to those of hay-fever, but occurring throughout the whole year and showing no connection with pollen. These people complain of frequent sneezing, and lachrymation; they have to blow their noses constantly; often they state that their attacks are most intense in the morning after leaving bed. In these cases the cause is nearly always to be sought in the gastro-intestinal tract. In other people, symptoms appear at irregular intervals during the day

and they suffer more in one place than in another. Then the cause has to be looked for in the inhalation of some irritating substance, often of protein nature. Frugoni and Ancona [88] found that feathers of *certain* pillows contain allergic substances. Doctor Galjard, of Rotterdam, furnished us with analogous material which had caused rhinitis in two patients. After changing the pillows for others, the symptoms disappeared. The author has also seen some cases of rhinitis vasomotoria due simply to the inhalation of the dust of grain or straw containing mites. All merchants and dealers who receive large stocks of wares, packed with straw or similar material, and who complain of vasomotor rhinitis, should be tested with an extract of grain containing mites, applied to skin scarifications. Of course, if dust from this material is really the causative agent, the patients must be instructed to avoid places where the dust is present. However, in many professions this is impossible and treatment has to be started. As a rule we give subcutaneous injections of tuberculin and of the extract of grain containing mites. We have, however, the impression that desensitization with the allergic substance (viz., grain containing mites) is difficult to realize. This is a case in which diagnosis is easy and certain, but treatment often difficult. Change of surroundings, of course, gives immediate relief of symptoms. It may be added that the diagnosis of these cases is often extremely easy; if a bottle containing grain with mites, which may have been killed by heating, is kept ready in the consulting room, the only thing to be done is to keep the open bottle under the patient's nose, asking him to make some deep inspirations. Lachrymation, sneezing, and a feeling of uneasiness will set in after one or two minutes.

Besides the material mentioned, other *specific* causes of rhinitis exist. Sometimes the odor of flowers (not the pollen) causes rhinitis or migraine; other substances also may do the same. Treatment will have to consist of the avoidance of these substances. If this is impossible, specific or non-specific treatment may be tried according to the rules given in the first part of the book. It is worth remembering that ipecacuanha rhinitis or ipecacuanha asthma is a typical example of the conditions described here.

Treatment of the " frugal " form of rhinitis also usually gives good results. The cause may be a specific one, and it then has to be treated accordingly, but it is usually non-specific. The first thing to be tried is peptone treatment by mouth, as described in an earlier part of this book. Often this treatment suffices. Attention must be drawn to the circumstance that peptone has to be given exactly three-quarters of an hour before *each* meal and that nothing whatever may be eaten between meals. The effect of this therapy, for which the author cannot offer a definite explanation, is often astonishing. Sometimes only a partial success is obtained; we then prescribe fifteen drops of diluted hydrochloric acid in water, to be taken during and after each meal. Often the attacks will then disappear. Peptone treatment has to be continued for many months; then *gradually* the effect of omitting peptone before one meal, later before two meals, etc., may be tried. As a rule, after six months peptone may be omitted entirely.

The question why a factor doubtless arising in the alimentary canal gives rise to symptoms of rhinitis is difficult to answer. The author tends to the view that in these patients the mucous membranes of the gastro-intestinal tract are more permeable than usual, hence products occur in the circulation which are absent in normal individuals.

These products might be the direct cause of irritation of the conjunctiva and nose; however, it seems to be more probable that the action of these substances is not direct. but that they only augment the action of irritating substances of the nature of grain containing mites, or miasms, prevailing in the air. The following fact seems to support this view. We have sometimes noticed that persons showing a form of rhinitis which indicated a relation with alimentary factors, and which was later relieved by peptone treatment, did not show symptoms when staying in the mountains. Even in these alimentary cases, the miasmatic factors seem to act as causative agents too. It is clear that the reverse also might be true; it might be that alimentary products resorbed by the intestine are the real allergens, whereas the miasms serve only as augmenting factors.

Relative to peptone treatment, an observation made by us in two cases has to be given. We encountered two patients whose symptoms of rhinitis were undoubtedly worse after taking half a gramme of peptone (both Witte's and Armour's). Perhaps it should be assumed that the mucous membranes of their stomachs absorbed the peptone too quickly.

URTICARIA

Although cases of urticaria due to direct contact with the allergen certainly exist (for instance, the case mentioned on page 55), urticaria is as a rule caused by alimentary factors. Contrary to the case of rhinitis, in urticaria the cause is very often specific. In fact, urticaria after eating strawberries, lobster, or shrimps, has certainly offered the oldest cases of hypersensitiveness or of "*anaphylaxie alimentaire.*" Diagnosis and treatment of these

forms are easy. Often the diagnosis has been made by the patient or by his mother long ago, and treatment consists of the avoidance of the allergic food. This is practically impossible if hypersensitiveness to eggs or milk is present, as it is difficult to avoid taking small quantities of these if meals are taken away from home. Desensitization will then have to be effected. This may be done in two ways: first, a very small dose of the foodstuff may be taken three-quarters of an hour before eating a meal which contains the food. Cases are known in which this treatment gave lasting results so that the first dose could be omitted later, but cases are also described in which this form of treatment had to be continued for many years, as omission of the first dose resulted in an attack. Instead of taking a small quantity of the allergen, half a gramme of peptone may be taken.

The second form of treatment consists of taking a very small quantity of the foodstuff (sometimes only a few milligrammes), and gradually increasing the dose. This may also give complete desensitization.

Patients suffering from urticaria of known origin seldom come for consultation; those who present themselves often offer difficulties of diagnosis, and often, as in the case of rhinitis, no specific causative agent is found, only the impression is gathered that an alimentary factor is active. Treatment then has to be conducted as indicated for rhinitis vasomotoria.

Recently we have met some cases of urticaria who could not be influenced by the therapy indicated. We then proceeded to sulphur injections and had very good results. Nothing has to be added to the technique, as it is described under the head of asthma.

Not infrequently outbreaks of urticaria coincide with

the menstrual periods, in which case auto-hæmotherapy should be tried. The technique is simple. Blood is drawn from an arm vein of the patient into a ten-c. c. syringe and injected into the same patient intramuscularly before it has clotted. This is repeated weekly during six or eight weeks. It sometimes gives complete success; if it fails, other methods of non-specific treatment will have to be tried.

In all cases of urticaria calcium chloride given by mouth may be helpful, but very seldom will it give complete relief.

As with the other forms of allergy, so in urticaria, subcutaneous injection of adrenalin will cause the disappearance of the symptoms for three or four hours; sometimes an entire attack may be stopped with one injection.

ECZEMA

Eczemata will as a rule be treated by the dermatologists, but the practitioner of internal medicine will encounter them as allergic symptoms, either combined with asthma or alone. In the case of eczema due to allergic causes, much time must be spent in finding out the causative agent, which will usually be of external origin. Nearly everything, from hair water and hair combs, to fur and silk, in fact everything which comes into contact with the skin, must be taken into consideration, and sometimes the cause will be found, and avoidance of contact will be sufficient to cure the eczema.

However, in a number of cases no agent will be found, and it must be remembered that eczemata may undoubtedly be caused by miasms. I have seen some cases of very intense *Eczema faciei* which disappeared in a remarkably short time in mountain air and returned some days after

coming home. These forms of eczema the author has seen react very well to application of sulphur treatment. If this fails, other forms of non-specific treatment, including tuberculin treatment, may be tried. During the last two years we gave a combination of tuberculin and sulphur treatment as a routine method and found it satisfactory.

Eczema occurring in combination with asthma is treated as asthma.

The question whether an eczema has to be treated with ordinary dermatological methods or antiallergically will sometimes be difficult to decide. Some work has already been done on the relation of eczema to skin reactions with human dandruff. The results, which have so far been only briefly mentioned to the author, seem to indicate that certain forms of eczema show indeed a positive skin reaction with our extract of human dandruff. I believe that antiallergic treatment should be tried in these cases.

Finally, it may be mentioned that psoriasis has been treated by many authors with non-specific proteins. Instances of successful tuberculin treatment in psoriasis have been reported to the author.

ANGIONEUROTIC ŒDEMA, QUINCKE'S ŒDEMA

In recent years it has become clear that a number of cases of angioneurotic, or Quincke's, œdema should be considered as due to hypersensitiveness to some allergens.

McIlvaine Philips [86] has gathered some instances from the literature in which the eating of pork or fish caused Quincke's œdema. Skin reactions with the material were also positive. We have seen two cases, one due to ingestion of pork, one due to salicylic acid. McIlvaine Philips also relates that the same condition is sometimes found in young dogs after eating pork. Quincke's œdema may be

hereditary. If the causative agent is found, therapy is easy and consists of avoidance of the allergic foodstuff.

MIGRAINE AND EPILEPSY

Of the relation between migraine and epilepsy and allergy little is known. Doubtless cases exist in which the eating of a certain drug or foodstuff causes attacks of migraine or epilepsy in persons suffering from either of these diseases. Eggs, chocolate, boric acid, and other substances may act as allergens in these cases. Since we know that anaphylactic shock often produces heightened irritability of the central nervous system and violent convulsions in guinea-pigs, it is not difficult to understand that in some human beings outbreaks of allergy might produce epileptic attacks. According to the author's view, it is probable that in such cases a primary factor exists, which predisposes certain centres in the brain, and that the allergic reaction acts only as a secondary stimulus. The same may hold for migraine. Too little is known about this subject to justify a more ample discussion.

In any case the fact that allergy may sometimes result in attacks of epilepsy and migraine is not to be denied, and it should be considered in relation to the treatment of these diseases.

Antiallergic treatment of certain cases of epilepsy has been tried and some favorable results have been reported. The author finds that careful attempts with tuberculin treatment and other forms of non-specific treatment must be made. The case of migraine is a little clearer. First, it is known that climatic factors undoubtedly play a part here, and further, it is quite certain that alimentary factors also occur. The author saw in a few cases very good results from peptone treatment and in a number of cases

also of tuberculin treatment. Generally therapy will have to be conducted as described under urticaria.

INTRAVENOUS THERAPY IN ALLERGIC DISEASE

Manifold are the substances advocated for antianaphylactic or skeptophylactic intravenous treatment in asthma and other allergic diseases. Intravenous injections of calcium chloride (afenil), hypertonic NaCl, or glucose solutions, etc., have been advised. The author has used them sometimes in very difficult cases but has never seen much result. In slight cases this therapy was not necessary, since other measures sufficed. Frugoni and Ancona advocate afenil therapy in hay-fever; the author has had till now no personal experience of this.

Auld has advocated intravenous peptone injections in bronchial asthma, and reports good results. Theoretically there is no reason why peptone treatment, if effective when given by mouth or subcutaneously, should not be just as effective when given intravenously. So far there is nothing against this therapy.

Nevertheless the author cannot but feel that every intravenous injection given to an allergic may be dangerous. With all the difficulties and doubtful facts relative to these diseases, we must all agree that in these patients the colloidal equilibrium of the blood may easily be disturbed. Certainly this is a point which has been demonstrated without doubt by Widal's school (*v. sup.*). It is equally sure that nothing may so easily disturb the equilibrium as an intravenous injection. Since instances have been reported where the mere injection of glucose, or saline solution, or the injection of one drop of horse serum or of any ordinary dose of salvarsan, killed an asthmatic, and since I have seen that even *ingestion* of half a gramme of peptone may

cause attacks, and that intracutaneous injections of traces of allergen may be dangerous, I have taken the resolution never to give intravenous injections to an allergic patient, if they can possibly be avoided.

The therapy of allergic diseases, even if conducted by a physician well trained in these cases, will always remain a task which includes many more risks than occur in any other form of treatment of internal diseases. Therefore the author considers it to be undesirable to widen the risks by introducing intravenous injections into anti-allergic therapy.

* * *

Not long ago the diagnosis of bronchial asthma meant continuous dyspnœa for the patient, with injections of morphine if the attacks became unendurable. Bronchial asthma was considered to be an incurable disease, and most physicians paid very little attention to sufferers from it, who thus became easy victims to all sorts of quacks, sellers of patent medicines, and Christian Scientists, and the same may be said of many other forms of allergy.

Now this condition has been changed. We are not yet able to cure every case of asthma or urticaria or migraine, but the important fact is that the possibility of applying a real decisive treatment in these diseases has been opened. They are as a whole no longer to be considered as incurable diseases. This new state of affairs is due in a large degree to the work of Chandler Walker, Cooke, Coca, and other investigators mentioned above. The present author is especially anxious to emphasize this point, since he has had on several occasions to disagree with some of their opinions, and he wishes to state definitely that, although

doing so, he fully recognizes the importance of the pioneer work which has been done by them.

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